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Proposed Registration Decision PRD2013-01

Chlorfenapyr

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Overview

Proposed Registration Decision for Chlorfenapyr

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Chlorfenapyr Technical Insecticide, Mythic Insecticide and Pylon Miticide Insecticide, containing the technical grade active ingredient chlorfenapyr. Mythic Insecticide is intended for use in limited applications to the exterior of buildings against various pests and as a pre-construction and post-construction termiticide. Pylon Miticide Insecticide is intended for use on greenhouse ornamentals and greenhouse fruiting vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Chlorfenapyr Technical Insecticide, Mythic Insecticide and Pylon Miticide Insecticide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on chlorfenapyr, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on chlorfenapyr, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Chlorfenapyr?

Chlorfenapyr is a member of the pyrrole class of insecticides (Group 13) and is the active ingredient contained in the commercial class products Pylon Miticide Insecticide and Mythic Insecticide. Pylon Miticide Insecticide is an insecticide/acaricide/nematicide for use on greenhouse ornamentals and some greenhouse fruiting vegetables. Mythic Insecticide is for use in limited applications to the exterior of buildings against various pests and as pre-construction and post-construction termiticide.

Health Considerations

Can Approved Uses of Chlorfenapyr Affect Human Health?

Products containing chlorfenapyr are unlikely to affect your health when used according to label directions.

Potential exposure to chlorfenapyr may occur through the diet, when handling and applying the product, or when entering an area that has been treated with the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

In laboratory animals, the technical grade active ingredient chlorfenapyr was of high acute toxicity by the oral route; consequently, the hazard signal words "DANGER POISON" are required on the label. Chlorfenapyr was of low acute toxicity by the dermal route, and moderately toxic by the inhalation route. Chlorfenapyr was mildly irritating to the eyes, non-irritating to skin and did not cause an allergic skin reaction.

The acute toxicity of the end-use products Mythic Insecticide and Pylon Miticide Insecticide was moderate by the oral and inhalation routes; consequently the hazard signal words "WARNING POISON" are required on the product labels. The acute toxicity of the end-use products was low by the dermal route. The end-use products were non-irritating to the eye, minimally irritating to the skin, and did not cause allergic skin reactions.

There was no evidence to suggest that chlorfenapyr damaged genetic material. Health effects in animals given repeated doses of chlorfenapyr included reductions in body weight, body weight gain and food consumption, deaths, and effects on the liver, blood, and nervous system. Chlorfenapyr also caused tumors originating from the blood production system in rats.

When chlorfenapyr was given to pregnant or nursing animals, deaths were observed in offspring at doses that were not toxic to the mother, indicating that the young were more sensitive to chlorfenapyr than the adult animal. The risk assessment takes this sensitivity into account in determining the allowable level of human exposure to chlorfenapyr.

Deaths occurred in adult animals at lower doses when chlorfenapyr was given by the inhalation route compared to the oral route. Toxicity via the inhalation route has not been characterized in developing fetuses or in young animals, and therefore extra protective factors were applied in the risk assessment to further reduce the allowable level of human exposure to chlorfenapyr via the inhalation route.

The risk assessment protects against the effects of chlorfenapyr by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Food

Dietary risks from food are not of concern

Dietary intake estimates based on the greenhouse residue trials, revealed that the children between 1-2 years old, the subpopulation which would ingest the most chlorfenapyr relative to body weight, are expected to be exposed to less than 21% of the acute reference dose, based on an intermediate refinement of the exposure. For the basic chronic dietary risk the children between 3-5 years old are expected to be the most affected subpopulation with an estimated exposure of 21% of the acceptable daily intake. Based on these estimates, the acute and chronic dietary risk from chlorfenapyr are not of concern for all population sub-groups.

The lifetime cancer risk estimate was further refined using American monitoring data. Based on this data, the lifetime cancer risk is not of concern (9×10^{-8}).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using chlorfenapyr on fruiting vegetables were acceptable. The proposed MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Risks in Residential and Other Non-Occupational Environments

Residential exposure after a termiticide treatment using Mythic Insecticide is not expected to result in unacceptable risk when used according to label directions. Residential exposure to individuals contacting treated outdoor surfaces is not expected to result in unacceptable risk when Mythic Insecticide is used according to label directions.

Residential exposure is not expected from use of Pylon Miticide Insecticide.

Occupational Risks From Handling Mythic Insecticide and Pylon Miticide Insecticide

Occupational risks are not of concern when Mythic Insecticide or Pylon Miticide Insecticide is used according to the label directions, which include precautionary measures, limitations on equipment usage and/or reductions in application rates.

Farmers and custom applicators who mix, load or apply Pylon Miticide Insecticide as well as workers re-entering freshly treated greenhouses can come in direct contact with product residues on the skin or through inhalation. Therefore, the label specifies that anyone mixing/loading and applying Pylon Miticide Insecticide must wear coveralls over long-sleeved shirt, long pants, shoes and socks and chemical resistant gloves. The label also requires that workers not enter the treated greenhouse for 12 hours after application. Based on the assessment of acute inhalation hazards, workers mixing/loading/applying Pylon Miticide Insecticide must wear a respirator. Taking into consideration these precautionary statements, restrictions on the maximum application rate and reduced number of applications, limiting application equipment and limiting the amount of product used, risks to these individuals are not of concern.

Pest control operators (PCOs) who mix, load, and apply Mythic Insecticide can come into direct contact with product residues on the skin or through inhalation. Therefore, the label specifies that anyone mixing/loading and applying Mythic Insecticide must wear a long-sleeved shirt, long pants, shoes and socks, and chemical resistant gloves. Similar to the Pylon Miticide Insecticide, the assessment of acute inhalation hazards warrants that mixers, loaders and applicators wear a respirator when applying in confined spaces. PCOs using mechanically pressurized handheld

equipment cannot mix/load and apply more than 80 L of product per day. The label also requires that no contact with treated areas can occur until sprays have dried.

For bystanders, exposure is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Chlorfenapyr Is Introduced Into the Environment?

Chlorfenapyr is toxic to pollinators such as honeybees and beneficial arthropods (i.e. predatory mite and parasitic wasp). Chlorfenapyr is persistent and immobile in soil, and is persistent in aquatic sediment. Label instructions that caution users about the potential effects of chlorfenapyr on non-target beneficial insects are required.

Due to the intended use pattern for Mythic Insecticide (indoor and structural uses) and Pylon Miticide Insecticide (greenhouse uses), limited environmental exposure is expected. However, once it enters the terrestrial environment, it is persistent and immobile. It is stable to hydrolysis and forms only minor phototransformation and biotransformation products on soil. Chlorfenapyr phototransforms in water, with the production of one major aquatic phototransformation product (CL 357806).

Chlorfenapyr is persistent in aquatic systems, undergoing slow biotransformation, with the production of one major aquatic biotransformation product under both aerobic and anaerobic conditions (CL 312094). Based on its low volatility (low vapour pressure and Henry's law constant), chlorfenapyr residues are not expected in the air, nor is long-range aerial transport expected.

Chlorfenapyr may adversely affect non-target terrestrial invertebrates, such as pollinators and beneficial arthropods. Therefore, toxicity statements as well as instructions that direct users not to apply the product in the presence of these sensitive and important insects, are specified on the product label.

Value Considerations

What Is the Value of Pylon Miticide Insecticide?

Pylon Miticide Insecticide controls a variety of arthropod and nematode pests on ornamentals and suppresses a variety of arthropod on some greenhouse fruiting vegetables.

Chlorfenapyr is a new mode of action (MOA) for use on greenhouse ornamentals and greenhouse fruiting vegetables, and will therefore provide a new tool for rotation with currently registered products in other mode of action groups. Pylon Miticide Insecticide is the only product registered for suppression of foliar nematodes on greenhouse ornamentals and tomato hornworm and tobacco budworm on greenhouse fruiting vegetables.

What Is the Value of Mythic Insecticide?

Mythic Insecticide kills a variety of arthropod pests when applied as a crack and crevice or spot treatment to the exterior of buildings where pests may enter (for example, doors, windows, around vents). Mythic Insecticide is also a pre- and post-construction termiticide.

The active ingredient in Mythic Insecticide has a different mode of action than currently registered pest control products used in structural pest control and will contribute to resistance management. It is also an alternative to older chemistries, such as organophosphates and carbamates, registered for the same uses. In addition, Mythic Insecticide will be an additional product that can be used against structural pests for which there are few products registered in Canada, such as subterranean termites.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Mythic Insecticide and Pylon Miticide Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with workers coming into direct contact with Mythic Insecticide and Pylon Miticide Insecticide on the skin or through inhalation of spray mists, anyone mixing, loading and applying these products must wear a long-sleeved shirt, long pants, shoes and socks, and chemical resistant gloves. In addition, for Pylon Miticide Insecticide, mixers/loaders and applicators must wear coveralls. The label also requires that workers not enter the treated greenhouses for 12 hours after application. The use pattern for Pylon Miticide Insecticide applied to greenhouse vegetables will be reduced to a single application per crop cycle at 0.075 g a.i./L assuming a maximum spray volume of 1000 L. Pylon Miticide Insecticide cannot be applied with mechanically pressurized handheld equipment to greenhouse ornamentals. The maximum spray volume for greenhouse ornamentals is 1500 L/ha. For Mythic Insecticide, workers must not mix, load and apply more than 80L of product/day with mechanically pressurized handheld equipment. Further to this, based on the assessment of acute inhalation hazards, workers mixing/loading Mythic Insecticide must wear a respirator and workers mixing/loading/applying Pylon Miticide Insecticide must wear a respirator.

Environment

Mitigative environmental label statements are required on all Pylon Miticide Insecticide labels. These statements will indicate the toxicity of chlorfenapyr to pollinators and beneficial arthropods, and direct users not to apply the product in their presence.

Next Steps

Before making a final registration decision on chlorfenapyr, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed maximum residue limits (MRLs) will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

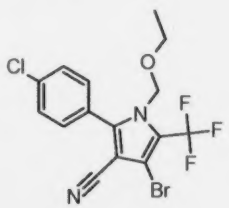
When the PMRA makes its registration decision, it will publish a Registration Decision on chlorfenapyr (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Chlorfenapyr

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Chlorfenapyr
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-1H-pyrrole-3-carbonitrile
2. Chemical Abstracts Service (CAS)	4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile
CAS number	122453-73-0
Molecular formula	$C_{15}H_{11}BrClF_3N_2O$
Molecular weight	407.62
Structural formula	
Purity of the active ingredient	97.1 % nominal

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—Chlorfenapyr Technical

Property	Result
Colour and physical state	pale yellow powder
Odour	odourless
Melting range	100–102.3 °C
Boiling point or range	not applicable to a solid
Density	1.6 g/cm^3
Vapour pressure at 25°C	5.40 × 10^{-6} Pa (estimated)
Henry's law constant at 20°C	8.22 × 10^{-6} atm-m^3- mol^{-1}
Ultraviolet (UV)-visible spectrum	λ (nm) ε (L mol^{-1} cm^{-1}) 200 40 × 10^3 260 10 × 10^3 300 2.0 × 10^3 negligible absorption observed above 310 nm
Solubility in water at 20°C (mg/L)	pH 5 buffer at 20 °C 0.11 pH 7 buffer at 20 °C 0.11 pH 9 buffer at 20 °C 0.14 deionised water at 10 °C 0.11 deionised water at 20 °C 0.14 deionised water at 30 °C 0.20
Solubility in organic solvents at 20°C (g/100 mL)	Solvent Solubility Hexane 0.685 Methanol 5.06 Acetonitrile 39.4 Toluene 49.0 Ethyl Acetate 51.4 Acetone 69.7 Dichloromethane 74.4
n-Octanol–water partition coefficient (K_{ow})	pH log K_{ow} 5 5.21 7 5.24 9 5.28

Property	Result
Dissociation constant (pK_a)	No groups ionisable in the environmental pH range.
Stability (temperature, metal)	Not sensitive to oxidizing or reducing agents, water, or monoammonium phosphate. Not impact sensitive or explosive as a dust, decomposes exothermally at 183°C.

End-use Product—Mythic Insecticide

Property	Result
Colour	tan
Odour	mild sweet odour
Physical state	liquid
Formulation type	suspension
Guarantee	Chlorfenapyr 240 g/L nominal
Container material and description	HDPE jugs
Density	1.11 g/mL
pH of 1% dispersion in water	7.06
Oxidizing or reducing action	Reacts with strong oxidizing agents.
Storage stability	Stable on storage in HDPE for 12 months
Corrosion characteristics	Not corrosive to HDPE
Explodability	Not impact sensitive, not expected to be thermally sensitive

End-use Product—Pylon Miticide Insecticide

Property	Result
Colour	tan
Odour	mild sweet odour
Physical state	liquid
Formulation type	suspension
Guarantee	Chlorfenapyr 240 g/L nominal

Property	Result
Container material and description	HDPE jugs
Density	1.11 g/mL
pH of 1% dispersion in water	7.06
Oxidizing or reducing action	Reacts with strong oxidizing agents.
Storage stability	Stable on storage in HDPE for 12 months
Corrosion characteristics	Not corrosive to HDPE
Explodability	Not impact sensitive, not expected to be thermally sensitive

1.3 Directions for Use

Pylon Miticide Insecticide is a commercial class insecticide, acaricide and nematicide to be used as a foliar treatment on greenhouse ornamentals and some greenhouse fruiting vegetables to control a variety of arthropod and nematode pests.

On greenhouse ornamentals, Pylon Miticide Insecticide controls two-spotted spider mites, cabbage looper, soybean looper, foliar nematodes and Western flower thrips at concentrations ranging from 20 to 156 ml product per 100 L of water (See Appendix I, Table 20). Spray volume is not to exceed 1500 L/ha. Pylon Miticide Insecticide can only be applied three times in a crop cycle with a minimum reapplication interval of 5 days.

On greenhouse fruiting vegetables, Pylon Miticide Insecticide suppresses tomato hornworm, tobacco budworm, cabbage looper, alfalfa looper and two-spotted spider mite at concentrations ranging from 20 to 30 ml product per 100 L of water (See Appendix I, Table 20 for exact concentration for each pest). Spray volume is not to exceed 1000 L/ha. Pylon Miticide Insecticide can only be applied once in a crop cycle.

Mythic Insecticide (240 g/L chlorfenapyr) kills ants, Asian ladybird, boxelder bugs, centipedes, European earwigs, house crickets, house flies, paper wasps, pillbugs, silverfish and spiders at concentrations of chlorfenapyr from 0.125 to 0.50% (See Appendix I, Table 21 for exact concentration for each pest). For these pests, it is applied as a crack and crevice or spot treatments to the exterior of buildings where the pests may enter (for example, doors, windows, around vents). In addition, Mythic Insecticide can be used both pre-construction and post-construction for the control of subterranean termites at 0.125-0.25%.

1.4 Mode of Action

Chlorfenapyr is a member of the pyrrole class of insecticides (Group 13). It works by uncoupling oxidative phosphorylation, preventing conversion of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). This causes the target pest to stop feeding shortly after exposure and die from inability to generate its own energy.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Chlorfenapyr Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulations has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

A gas chromatography method using an electron capture detector (GC-ECD) was developed and proposed for data generation and enforcement purposes. This method fulfilled the requirements with regards to selectivity, accuracy and precision at the respective limit of quantitation. Acceptable recoveries (70-120 %) were obtained in environmental (soil) media. Methods for residue analysis are summarized in Appendix I, Table 1.

The quantitation of chlorfenapyr, by analytical method M2427, was accomplished by gas chromatography equipped with an electron capture detector (GC-ECD). For certain commodities, standards and samples were analyzed using a slightly different temperature programming of the GC to isolate impurity peaks. Capillary gas chromatography (GC) using a mass selective detector (MSD) in selective ion monitoring mode (SIM) or nitrogen phosphorus detection (NPD) may be used for residue confirmation. The quantitation was performed using external standards with a validated limit of quantitation (LOQ) of 0.05 ppm for each commodity except for tomato juice, potato, and potato processed commodities, which is 0.01 ppm. This method fulfilled the requirements with regards to specificity, accuracy and precision at the lowest LOQ. Acceptable recoveries (76-113%) were obtained in plant matrices. The extraction efficiency of the solvent system employed in the analytical method M2427 was validated using tomato samples with bioinccured residues of chlorfenapyr, collected from the metabolism study. The extractabilities were comparable (81-82%).

No analytical method for the determination of chlorfenapyr residues in animal matrices are required, as there are no feed items derived from the petitioned crops.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Chlorfenapyr is a pro-insecticide belonging to the halogenated pyrrole class of compounds. Chlorfenapyr is converted to an N-dealkylated pesticidally active metabolite, which acts to uncouple oxidative phosphorylation in the mitochondria of insects via disruption of the proton gradient.

A detailed review of the toxicological database for chlorfenapyr was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The majority of the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is acceptable and the database is considered adequate to define the majority of toxic effects that may result from exposure to chlorfenapyr.

Oral metabolism studies were conducted with radiolabeled chlorfenapyr administered to rats via gavage dosing as a single oral low dose, a single oral high dose, or as a repeated low dose for 14 days. These studies indicated that absorption of chlorfenapyr via the oral route was low as >80% of the administered dose was excreted in the feces, only 4-10% was excreted in the urine, and radioactivity levels in expired air were negligible. It should be noted, however, that biliary cannulation experiments were not available, nor was an assessment of plasma kinetics conducted. The majority (80-90%) of the administered dose was excreted within the first 48 hours post-dosing, and there were no major differences with respect to sex, dose regimen or radiolabel position for the excretion profile. The highest levels of radioactivity were detected in the fat, liver and blood, while the brain showed the lowest concentration of radioactivity. Levels of radioactivity in tissues of females were higher than males. Repeated exposure did not increase the level of radioactivity in tissues. Radioactivity levels in tissues in the high dose group (200 mg/kg bw) were 5-6 times higher than the values at the low dose level (20 mg/kg bw). The proposed metabolic pathway involved cleavage of the ethoxymethyl side-chain, followed by dealkylation and ring hydroxylation, and some degree of conjugation of the de-alkylated, ring-hydroxylated metabolites. The bond between the phenyl and pyrrole rings remained intact. The major metabolites were N-dealkylated, debrominated and hydroxylated products, as well as their conjugated forms. The parent compound was not detected in urine, but was the major compound detected in feces (40-70% of the administered dose). Several common metabolites were detected in the urine, feces and/or tissues, and there were no major differences in metabolite profile in excreta or tissues with respect to sex, dose regimen or position of radiolabel.

In acute toxicity studies, chlorfenapyr technical was highly toxic to rats and mice via the oral route, of low toxicity via the dermal route in rabbits and moderately toxic via the inhalation route in rats. Chlorfenapyr was mildly irritating to the eyes of rabbits, non-irritating to skin of rabbits and was not considered to be a potential dermal sensitizer based on findings from a guinea pig Maximization test.

Acute toxicity studies were conducted with the end-use products Mythic Insecticide and Pylon Miticide Insecticide (containing approximately 22% chlorfenapyr). These end-use products were moderately toxic via the oral route in rats, of low toxicity via the dermal route in rabbits and moderately toxic via the inhalation route in rats. The end-use products were non-irritating to the eyes of rabbits, minimally irritating to the skin of rabbits, and were not considered to be potential dermal sensitizers based on the results of a Buehler test conducted in guinea pigs.

Mortality was a common endpoint throughout the chlorfenapyr toxicity database. Treatment-related deaths were observed in adult animals in the rat and mouse dietary, rat 90-day inhalation, rat acute neurotoxicity, and rabbit developmental toxicity studies. Pre- and/or post-natal mortality was also observed in the rat reproductive toxicity and developmental neurotoxicity (DNT) studies, as well in the rabbit developmental toxicity study. The treatment-related mortalities occurred following one or two doses in many of the studies. There was an apparent difference between species with regards to sensitivity with the rabbit appearing to be the most sensitive, followed by the mouse and rat. The findings in the dog studies suggested that the dog was the least sensitive to this effect, as no mortalities were observed at a dose level that caused substantial decreases in body weight and bodyweight gain. However, this was confounded by potential issues with palatability. In adult animals, other evidence of systemic toxicity (such as liver findings and/or effects on body weight or food consumption) was generally observed at doses below that at which mortality was observed. However, in the DNT study, pup mortality occurred at the lowest observable adverse effect level (LOAEL) and in the absence of maternal toxicity. In comparing the mortality data across the available toxicity studies, it was apparent that deaths occurred at substantially lower dose levels in young animals compared to adults. For example, adult female rats tolerated doses of up to 350 mg/kg bw/day via gavage administration for eight days in the developmental toxicity range-finding study without any treatment-related deaths, while increased pup deaths occurred in the DNT study during post-natal days (PND) 0-4 when dams were dosed at 10 mg/kg bw/day via gavage administration (no observable adverse effect level (NOAEL) of 5 mg/kg bw/day). These findings demonstrated increased susceptibility of young animals to chlorfenapyr-induced mortality.

Other findings in repeat-dose studies with mice and rats included decreased body weight, body weight gain and food consumption, liver toxicity (increased weight and hepatocellular hypertrophy, accompanied by elevated liver enzymes in some studies) and alterations in clinical chemistry and haematology parameters. The liver effects were noted across species (mouse, rat and rabbit) and routes (dietary, gavage, dermal and inhalation), and usually occurred at or below the LOAEL of the study, and on their own were generally considered to be indicative of an adaptive response rather than adverse. The changes in clinical chemistry parameters included increases in blood urea nitrogen, decreases in albumin, and increases in cholesterol levels in rat studies. Haematology findings included increased white blood cell counts in mice and rats, as well as decreases in haemoglobin, hematocrit and/or red blood cell counts in rats.

Central and peripheral nervous tissues were also a target of chlorfenapyr toxicity in the mouse and rat. The predominant finding was vacuolation of the spinal cord and white matter of the brain. This finding was noted in adult mice of both sexes in 90-day and 18-month dietary studies, in adult male rats in 90-day and 12-month neurotoxicity dietary studies, as well as in pups of both sexes in the rat DNT study. In most of the studies, the neuropathological findings occurred

at the study LOAEL, with the exception of the 90-day mouse and rat DNT studies, in which these findings occurred at the next higher dose level. Vacuolation was also noted in the optic and sciatic nerve of adult male rats in the 90-day study at the highest dose level tested. It should be noted that brain tissue was not examined in the 28-day dietary studies in both the rat and mouse, and therefore it is not known whether neuropathological lesions would have been detected following shorter-term dosing. The neuropathological lesions appeared to be at least partially recoverable based on findings in a 16-week recovery period at the end of the 12-month dietary neurotoxicity study in the rat. Also, in the DNT study, in which dosing ends at PND 21, nervous tissue vacuolation was observed in PND 22 pups, but not PND 62 pups which had experienced a 40-day period without dosing.

As nervous tissue was a target of toxicity, acute, 12-month and developmental neurotoxicity studies were conducted in the rat. Neurotoxicity batteries were also included in the 90-day inhalation and 28-dermal rat studies. In the acute neurotoxicity study, decreased motor activity, lethargy and altered tail pinch response were noted at the study LOAEL, and decreased arousal, decreased grip strength, and altered gait and finger snap responses were observed at the highest dose level, along with mortality. In the 12-month neurotoxicity study, in addition to vacuolation of the brain and spinal cord noted in males at the study LOAEL, decreased grip strength was also noted in males at the highest dose level. Effects noted during the neurotoxicity assessment in the 90-day inhalation study included increased motor activity and rearing at the study lowest observed adverse effect concentration (LOAEC) in males. Effects at the highest dose level included decreases in hind limb grip strength (males) and rearing (females), as well as mortality (males). In the 28-day dermal study, piloerection and decreased rearing were noted in females at the study LOAEL (which was the highest dose level tested).

In the DNT study, there was an increase in pup mortality (PND 0-4) at the study LOAEL, as noted above. These deaths occurred while the only source of exposure to chlorfenapyr was through lactation, as direct dosing of pups began on PND 11. Other effects in pups at the study LOAEL included decreased motor activity in both sexes (at PND 13) and effects on learning in an M-water maze in males. The learning effects were characterized by a decrease in the mean number of males successfully performing a 're-learning' task at PND 23. In addition, males at the LOAEL failed to demonstrate improvement in the time to complete the 're-learning' task at PND 60. At the highest dose level, effects were noted in males in the auditory startle test (increased peak amplitude and latency at PND 24). Vacuolation of brain tissue (frontal lobe, parietal lobe, midbrain, pons, cerebellum and medulla oblongata) in PND 22 pups (both sexes) and changes in morphometric measurements in brain tissue in both sexes were also observed at the highest dose level. The morphometric changes included decreases in corpus callosum and cerebellum measurements (in PND 22 and 62 males), and decreases in hippocampus measurements (in PND 62 females). All of the findings in offspring in the DNT study occurred at a dose level that did not cause any signs of maternal toxicity, which, as noted above, provided evidence of increased susceptibility of the young.

Twelve-month and 90-day dietary dog studies were available. The main findings in these studies were decreased body weight and food consumption, which may have been attributed to a palatability issue, as well as an increase in lymphoid follicles in the stomach of dogs which were administered chlorfenapyr for 12 months.

Dermal toxicity studies (28-day) were conducted in the rat and rabbit, and a 90-day inhalation study was conducted in the rat. The rabbit dermal study, which was considered to be supplemental due to the omission of organ weight and histopathology data for several tissues required under current guidelines, revealed liver findings (increased weight, vacuolation and discoloration) and altered clinical chemistry parameters. In the rat dermal study, adverse findings were only noted at the highest dose level, and included urine staining and altered clinical chemistry parameters in both sexes, as well as increased piloerection and decreased rearing in females. In the 90-day inhalation study, evidence of systemic toxicity included decreased testes and epididymis weights at the study LOAEC. Effects at the highest dose level included, increased respiration rates, altered haematology parameters in both sexes, mortality in males, and increased lung, liver and ovarian weights in females. The highest dose level originally included in the inhalation study had to be terminated due to the high incidence of mortality in males observed within 3-4 exposures.

Based on the mortality data, there was evidence that the inhalation route was more toxic than the oral route. In the 90-day inhalation study, treatment-related deaths were observed in males at 11 mg/kg bw/day and above, whereas in the 90-day dietary study, no deaths were observed at the highest dose tested (92/103 mg/kg bw/day for males/females). In the 28-day dietary study, deaths were only noted in males at 243 mg/kg bw/day (NOAEL for mortality in males of 177 mg/kg bw/day). There was clear evidence from studies conducted via the oral route that young animals were more susceptible to the toxicity of chlorfenapyr and that the inhalation route was more toxic than the oral route. However, the toxicity of the susceptible subpopulation (i.e. the young) via the inhalation route has not been characterized, and based on the available data, it is anticipated that mortality in young animals would occur at a lower dose level compared to adult animals when exposed via the inhalation route. This concern has been addressed through the application of a database uncertainty factor when assessing risks resulting from inhalation exposures.

Developmental toxicity was investigated in rats and rabbits. In the rat study, maternal toxicity was limited to decreases in food consumption and body weight gain. Findings in the fetus occurred only at the highest dose level tested, and were all related to ossification. There was an increased incidence of unossified sternebrae; however, the overall combined incidence of unossified and/or incompletely ossified sternebrae was comparable to controls, and therefore concern for this finding was low. There was also a slight increase in the number of rib pairs and thoracic ossification sites, and a corresponding decrease in lumbar ossification sites in fetuses. In the range-finding developmental toxicity study in the rabbit, maternal mortality was noted at the mid dose level, and there was evidence of abortion at the highest dose level. At the mid dose level, there was also a decrease in fetal weight. In the main rabbit study, slight decreases in body weight gain and food consumption were noted in maternal animals, and at the same dose level there was a decrease in the number of fetuses per dam, as well as increases in post-implantation loss and the number of early resorptions. As these serious effects in the fetus occurred at a dose level associated with only marginal toxicity in maternal animals, the results from the rabbit study provided evidence of increased susceptibility of the young.

Reproductive toxicity was investigated in range-finding and full 2-generation studies in the rat. In the range-finding study, parental toxicity was limited to decreases in body weight and food consumption during premating at or above the mid dose level. In offspring, there was a slight decrease in the viability index (on a pup basis only; no increase in mortality on a litter basis) at the mid dose level, as well as decreases in pup weight during lactation and an increased incidence of pup mortality (on a pup and litter basis) during PND 0-4 at the highest dose level. In the 2-generation study, parental toxicity included effects on body weight, body weight gain and food consumption. At the mid dose level, body weight and body weight gain were decreased only in Parental generation males during premating. Maternal effects were only noted at the highest dose level tested, and included decreases in food consumption during premating and gestation (P generation), and decreases in body weight gain during premating (P and F_1 generations), gestation (F_1 generation) and lactation (P generation). P generation females also had decreased body weights during gestation at the highest dose level. In offspring, there was a decrease in pup weight during lactation in both generations at the mid dose level, and an increase in the incidence of stillbirths and pup mortality during PND 0-4 at the highest dose level tested. In both studies pup mortality was noted at a dose level associated with less severe parental toxicity (effects on body weight and/or food consumption). It should be noted that these studies were missing some parameters required in the current reproductive toxicity guidelines, including sperm and follicle assessments, as well as organ weights. Brain tissue was also not examined in the reproductive toxicity studies; however, a full assessment of nervous tissue of dams and pups was included in the DNT study.

There was some evidence of effects on reproductive tissues of rats elsewhere in the toxicology database for chlorfenapyr. In the 28-day dietary study, aspermiogenesis was noted in a few males at a relatively high dose level. In the 90-day dietary study, testicular atrophy and increases in ovarian/uterine weight were observed at the study LOAEL, while prostate and seminal vesicle atrophy and mammary gland cysts were noted at the highest dose level tested. In the 90-day inhalation study, decreased testes and epididymal weights were noted at the study LOAEC, and increased ovarian weights were observed at the highest dose level. In the 24-month rat dietary study, there was an increase in testes weight accompanied by an increased incidence of testicular hyperplasia at the highest dose level tested. Residual concern for these findings was low since the risk assessment provided substantial margins to the dose levels at which these effects were observed.

Chlorfenapyr was tested in a battery of in vitro and in vivo genotoxicity studies. There was no evidence in any of these studies that chlorfenapyr had genotoxic potential. In an 18-month mouse dietary oncogenicity study, there was no evidence of treatment-related tumours. However, in the 24-month rat dietary chronic toxicity/oncogenicity study, there were treatment-related increases in tumours of the hematopoietic system in males. The incidences of histiocytic sarcomas and lymphocytic lymphomas were increased at the high dose level, and were commonly identified as the cause of/or contributing to the deaths of animals in which they were found. These tumours were detected in several tissues in each affected animal. The tissue types varied, most commonly including the liver, lymph nodes, bone marrow, spleen and thymus. The incidence of histiocytic sarcomas and lymphocytic lymphomas in high dose males exceeded the historical control ranges, and were statistically significantly increased compared to concurrent controls in high dose males.

Linear low dose extrapolation assessments were conducted for these tumours, the results of which were used for the cancer risk assessment for chlorfenapyr.

Acute oral toxicity and genotoxicity studies were available for several metabolites of chlorfenapyr. An acute oral toxicity study was conducted with AC 312,094, a soil and plant metabolite, the results of which suggested that this compound was of low acute toxicity in the rat. Ames tests were conducted with AC 312,094, CL 303,268 (the pesticidally active metabolite; which also appears in the rat metabolite studies) and CL 322,250 (a metabolite in ruminant meat byproducts). All three of these genotoxicity tests were negative.

Results of the toxicology studies conducted on laboratory animals with chlorfenapyr and its associated end-use products are summarized in Appendix I, Table 2 and Table 3. Results from toxicity studies conducted with metabolites of chlorfenapyr are summarized in Appendix I, Table 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from Canada and the United States were searched and reviewed for chlorfenapyr.

As of July 10, 2012, two human and 11 domestic animal incidents and involving chlorfenapyr were located in the PMRA database, all of which occurred in the United States (2010-12). One of the human incidents was a death associated with an accidental poisoning, and the other involved an adult who required hospitalization for a fall resulting from light-headedness possibly related to the use of a chlorfenapyr product. Two incidents of respiratory symptoms (including wheezing and respiratory distress) associated with indoor applications of chlorfenapyr were also reported in California (2006-07).

3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for chlorfenapyr. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, as well as a developmental neurotoxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses compared to parental animals in the rat developmental toxicity study. In the rabbit developmental toxicity study, increased susceptibility of the fetus was evident as more serious effects (decreased number of fetuses per dam and increased number of early resorptions and post-implantation losses) were observed at dose levels that caused marginal decreases in body weight and food consumption in maternal animals. In the reproductive toxicity study, there was also evidence of sensitivity of the young as there was an increased incidence of pup mortality (PND 0-4) at a dose that caused decreased body weight gain in maternal animals. In the DNT study, increased pup mortality (PND 0-4) was noted at a dose that did not result in maternal toxicity, providing further evidence of sensitivity of the young. The effects in the DNT study occurred at a lower dose compared to those observed in the rabbit developmental toxicity or rat reproductive toxicity studies, and therefore this study was considered critical in characterizing susceptibility of the young to chlorfenapyr toxicity.

Overall, the database is adequate for characterizing pre- and post-natal effects and determining susceptibility of the young via the oral route. There was evidence of susceptibility of the young in the studies noted above. In the DNT study, a serious endpoint (mortality) was noted in pups shortly after birth at a dose level that did not cause toxicity in the adult animals. Therefore, the 10-fold *Pest Control Products Act* factor was retained when using the rat DNT study to establish the point of departure for assessing risk to women of child-bearing age, as well as to infants and children.

Although pre- and post-natal effects are well-characterized via the oral route, effects on the young are not sufficiently characterized via the inhalation route, which was more toxic to rats than the oral route. This lack of information has been taken into account through the application of a database uncertainty factor where relevant, as outlined below.

3.2 Acute Reference Dose (ARfD)

Females 13-49 Years of Age and Children up to 12 Years of Age

To estimate acute dietary risk for the above-noted subpopulations, the DNT study with a NOAEL of 5 mg/kg bw/day was selected for risk assessment. At the LOAEL of 10 mg/kg bw/day, an increase in pup mortality (PND 0-4) was observed. It was considered possible that these deaths were the result of a single exposure and are therefore relevant to an acute risk assessment. These deaths occurred while the only source of exposure to chlorfenapyr was through lactation (direct dosing of pups began on PND 11), providing evidence that the deaths in young animals could be the result of direct exposure to chlorfenapyr. In defining the relevant subpopulation for this effect, it is difficult to clearly correlate the developmental stage of a juvenile rat to a human child. Therefore, in assessing risks to children consuming chlorfenapyr through the diet, the mortality observed during the early post-natal period in the DNT study was deemed relevant for children up to 12 years of age. This effect was also considered relevant for assessing dietary risks to women of child-bearing age in order to protect the fetus as well as the nursing infant since the effect could not clearly be attributed to only early post-natal exposure and may also have been at least partially associated with in utero exposure. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been

applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the 10-fold *Pest Control Products Act* factor was retained when using the rat DNT study to establish the point of departure for assessing risk to women of child-bearing age, as well as to infants and children. **The composite assessment factor (CAF) is 1000.**

The ARfD is calculated according to the following formula:

ARfD (females 13-49 years of age and children up to 12 years of age)

$$= \frac{\text{NOAEL}}{\text{CAF}} = \frac{5 \text{ mg/kg bw}}{1000} = 0.005 \text{ mg/kg bw of chlorfenapyr}$$

General Population (excluding females 13-49 years of age and children up to 12 years of age)

To estimate acute dietary risk for the general population, the 90-day dietary mouse and the rabbit developmental toxicity (range-finding and main) studies were all considered to be critical studies for risk assessment. In the 90-day mouse study, two animals died within 2 days of dosing (at the 63/79 mg/kg bw/day dose level for males/females) and in the pilot rabbit developmental toxicity study, two dams died after a single dose of chlorfenapyr (50 mg/kg bw). The NOAELs for mortality were similar in these studies. In the 90-day dietary mouse study, the NOAEL for mortality was 28 mg/kg bw/day. In the main rabbit developmental toxicity study, no mortality was observed in dams at dose levels of up to 30 mg/kg bw/day, and in the range-finding rabbit developmental toxicity study, the NOAEL for mortality was 25 mg/kg bw/day. As the deaths in these studies occurred within the first two days of dosing, they are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. The *Pest Control Products Act* factor was reduced to 1-fold for this scenario since risks to pregnant and nursing women, as well as infants and children up to 12 years of age, are addressed in a population-specific ARfD (see above). **The composite assessment factor (CAF) is 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{30 \text{ mg/kg bw}}{100} = 0.3 \text{ mg/kg bw of chlorfenapyr}$$

3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the DNT study with a NOAEL of 5 mg/kg bw/day was selected for risk assessment. At the LOAEL of 10 mg/kg bw/day, an increase in pup mortality (PND 0-4) was observed. This study addressed the endpoint of concern (mortality) in the most sensitive subpopulation (the young). Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the 10-fold *Pest Control Products Act* factor was retained when using the rat developmental neurotoxicity study

to establish the point of departure for assessing risk to women of child-bearing age, as well as to infants and children. **The composite assessment factor (CAF) is 1000.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5 \text{ mg/kg bw/day}}{1000} = 0.005 \text{ mg/kg bw/day of chlorfenapyr}$$

The ADI provides a margin of greater than 500 to the NOAELs for vacuolation of the nervous tissue in rats (in the 12-month neurotoxicity study) and mice (in the 18-month dietary study). This ADI also provides margins of 4400-5200 to the NOAELs for testicular atrophy and increased ovarian/uterine weights in the 90-day rat dietary toxicity study, and margins of 3000 to the testicular effects noted in the 24-month rat dietary study.

Cancer Assessment

There were treatment-related increases in the incidences of hematopoietic system tumours (histiocytic sarcomas and lymphocytic lymphomas) in male rats. No information was submitted to discount the relevance of these tumours to humans, and therefore linear low dose extrapolation assessments were conducted to generate Q_1^* values for these tumours. The most conservative Q_1^* value was determined to be 1.56×10^{-2} $(\text{mg/kg bw/day})^{-1}$ for the histiocytic sarcomas, and this value was used for the cancer risk assessment for chlorfenapyr.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-, Intermediate- and Long-term Dermal

For dermal risk assessments of all durations, the rat DNT study was selected since the 28-day dermal toxicity studies, as well as studies of longer duration, did not address the endpoint of concern in the sensitive subpopulation (i.e. mortality of the young animal). Increased mortality of pups shortly after birth was noted at a dose level of 10 mg/kg bw/day and higher. The NOAEL in this study was 5 mg/kg bw/day.

For residential scenarios, the target margin of exposure (MOE) is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold *Pest Control Products Act* factor was retained. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed women.

For occupational scenarios, the target MOE is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant and nursing women, it is necessary to afford adequate protection of the fetus which may be exposed via its mother and to nursing infants who may be exposed through breast milk. In light of concerns regarding prenatal and postnatal toxicity (as outlined in the *Pest Control*

Products Act Hazard Characterization section), an additional 10-fold factor was applied to this endpoint. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-, Intermediate- and Long-term Inhalation

For inhalation risk assessments of all durations, the 90-day inhalation study in the rat was selected. Increased motor activity and rearing and decreases in testes and epididymis weights were observed at 5.4 mg/kg bw/day. Mortality was observed at the next dose (11 mg/kg bw/day) in males. The NOAEL in this study was 1.4 mg/kg bw/day.

The target MOE for all residential and occupational scenarios is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. Based on findings in the 90-day inhalation study in the rat, chlorfenapyr was more toxic via the inhalation route in adult animals. Also, as noted previously, the young animal was more susceptible to the toxic effects of chlorfenapyr than the adult. As there is no route-specific study addressing the endpoint of concern (mortality) in the sensitive subpopulation (the young animal), an additional 10-fold database uncertainty (UF_{DB}) factor was applied to the study NOAEL when using the 90-day rat inhalation study to establish the point of departure for assessing risk via the inhalation route to women of child-bearing age, as well as to infants and children. Although the NOAEL for mortality in the 90-day inhalation study was 5.4 mg/kg bw/day, the additional UF_{DB} factor was applied to the study NOAEL of 1.4 mg/kg bw/day when assessing risks via the inhalation route. In consideration of the concerns noted above, along with the fact that the available studies were conducted in the rat, which was not found to be the most sensitive species to the endpoint of mortality, the established margin to mortality in the inhalation study was considered necessary. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed women.

Combined MOE for Occupational Exposure Assessments

It was determined that mortality was a common endpoint via the dermal and inhalation routes. Therefore, it was considered appropriate to assess combined exposure via the dermal and inhalation routes for mixer/loader/applicators handling chlorfenapyr products, and to compare them to the endpoints and corresponding MOEs established for short- to long-term dermal and inhalation exposures as outlined above.

Incidental Oral Ingestion (Children, Short-term)

For incidental oral ingestion risk assessments of short-term duration for children, the DNT study was selected. Increased mortality of pups shortly after birth was noted at a dose of 10 mg/kg bw/day and higher. The NOAEL in this study was 5 mg/kg bw/day.

The target MOE is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold *Pest Control Products Act* factor was retained when using the rat developmental neurotoxicity study to establish the point of departure for assessing risk to infants and children.

Occupational exposure to both Mythic Insecticide and Pylon Miticide Insecticide is characterized as short- to long-term and is predominantly by the dermal and inhalation routes.

Residential exposure to Mythic Insecticide is expected to be short- to long-term and is predominantly by the dermal route for adults and dermal and incidental oral routes for children.

3.4.1.1 Dermal Absorption

Chemical specific dermal absorption data were submitted for chlorfenapyr. In the *in vivo* study, groups of rats were administered nominal doses of 0.0217 or 2.4 mg/cm^2 of chlorfenapyr and exposed for 8 hours. After the 8-hour exposure period, the semi-occlusive covers were removed and the skin was washed. Four rats, per dose level, were terminated at 8, 24, and 120 hours after dosing (n=24). Mean recoveries of radioactivity across the dose groups ranged from 92% to 105% with the majority of the radioactivity recovered in the skin wash. The final dermal absorption values included both the absorbed dose (urine, feces, cage wash, blood cells, plasma, and carcass) and absorbable dose (skin at application site, surrounding skin and second skin wash). The low dose had absorption values of 13.13%, 12.99%, and 15.52% at 8, 24 and 120 hours, respectively. At the high dose, absorption values at 8, 24 and 120 hours were 6.36%, 7.17%, and 3.94%, respectively.

A dermal absorption value of 16% was selected for occupational and residential risk assessments. The dermal absorption value may underestimate exposure to workers in greenhouses as the administered nominal doses are higher than greenhouse application rates. However, conservatisms in the dermal absorption value, such as the inclusion of skin-bound residues, mitigate this concern.

3.4.2 Occupational Exposure and Risk

A quantitative risk assessment was conducted for Mythic Insecticide for termiticide and outdoor structural uses and Pylon Miticide Insecticide for use on greenhouse ornamentals and vegetables. Risk estimates for greenhouse applicators and re-entry workers and PCOs were found to be acceptable provided mitigation measures are adopted.

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Non-Cancer Exposure and Risk Assessment

Exposure to workers mixing, loading and applying the products is expected to be short- to long-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying the products using mechanically pressurized handheld equipment, manually pressurized handwands or backpack sprayers. A mixer/loader only exposure scenario was determined acceptable for the termiticide use of Mythic Insecticide when applied with rodding (i.e. closed application system). The exposure estimates are based on mixers/loaders/applicators wearing long-sleeved shirt, long pants, shoes and socks and chemical resistant gloves and in addition for Pylon Miticide Insecticide, coveralls are worn over the single layer personal protection equipment (PPE).

Dermal and inhalation exposure estimates for workers were generated using the Pesticide Handlers Exposure Database (PHED), version 1.1 because chemical-specific data for assessing human exposures during pesticide handling activities were not submitted (Table 3.4.2.1.1). PHED is a compilation of generic mixer/loader and applicator passive dosimetry data which facilitate the generation of scenario-specific exposure estimates.

Table 3.4.2.1.1: PHED Dermal and Inhalation Unit Exposure Estimates for Workers Mixing, Loading and/or Applying Mythic Insecticide or Pylon Miticide Insecticide Using Proposed PPE

Scenario	Exposure (in µg/kg a.i. handled)	
	Dermal Exposure	Inhalation Exposure
Single Layer with Gloves – Mythic Insecticide		
M/L Open Pour	51.14	1.6
M/L/A Mechancially-pressurized handheld equipment	5585.49	151
M/L/A Manually-pressurized handwand	943.37	45.2
M/L/A Backpack	5445.85	62.1
Coveralls over Single Layer with Gloves – Pylon Miticide Insecticide		
M/L/A Mechanically-pressurized handheld equipment	2453.52	151
M/L/A Manually-pressurized handwand	735.22	45.2
M/L/A Backpack	2597.09	62.1

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by combining the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological end points (NOAELs) to obtain the MOE; the target MOE is 1000 (Table 3.4.2.1.2). When a backpack sprayer or mechanically pressurized handheld equipment is used to apply Mythic Insecticide or mechanically pressurized handheld equipment to apply Pylon Miticide Insecticide, the dermal MOEs do not exceed the target MOE of 1000. However, given the conservatisms assumed in the dermal absorption value and in the area treated per day (ATPD), the risk is considered acceptable for backpack sprayer. For Mythic Insecticide, the ATPD for the mechanically-pressurized handheld equipment scenario had to be reduced to 80L per day for MOEs to exceed the target.

Based on the assessment of acute inhalation hazards, workers mixing/loading Mythic Insecticide must wear a respirator and workers mixing/loading/applying Pylon Miticide Insecticide must wear a respirator. When considering the additional requirement for a respirator, the risk to mixer / loaders and applicators (M/L/A) using mechanically-pressurized handheld equipment on greenhouse vegetables becomes acceptable (Combined MOE = 904).

Table 3.4.2.1.2: Mixer/Loader/Applicator Dermal and Inhalation Exposure Estimates and MOEs (shaded cells indicate the target MOE is not exceeded).

	Scenario	ATPD (L/day)	Dermal Exposure (mg/kg bw/day)[a]	MOE[b]	Inhalation Exposure (mg/kg bw/day)[a]	MOE[b]	Combined MOE
Termiticide	M/L/A Mechanically-pressurized handheld equipment	80	2.89×10^{-3}	1730	4.88×10^{-4}	2870	1080
	M/L/A Manually-pressurized handwand	150	9.14×10^{-4}	5470	2.74×10^{-4}	5120	2640
	M/L/A Backpack	150	5.28×10^{-3}	948	3.76×10^{-4}	3720	756
	M/L Open Pour Rodding	757	2.50×10^{-4}	20000	4.89×10^{-5}	28600	11800
Greenhouse Ornamentals	M/L/A Mechanically-pressurized handheld equipment	3800	5.85×10^{-3}	855	2.25×10^{-3}	622	360
	M/L/A Manually-pressurized handwand	150	6.92×10^{-5}	72300	2.66×10^{-5}	52700	30500
	M/L/A Backpack	150	2.44×10^{-4}	20500	3.65×10^{-5}	38300	13300

Scenario		ATPD (L/day)	Dermal Exposure (mg/kg bw/day)[a]	MOE[b]	Inhalation Exposure (mg/kg bw/day)[a]	MOE[b]	Combined MOE
Greenhouse Fruiting Vegetables	M/L/A Mechanically-pressurized handheld equipment	3800	4.86×10^{-3}	1030	1.87×10^{-3}	749	433
	M/L/A Manually-pressurized handwand	150	5.75×10^{-5}	87000	2.21×10^{-5}	63400	36700
	M/L/A Backpack	150	2.03×10^{-4}	24600	3.03×10^{-5}	46100	16100

[a] Dermal/Inhalation Exposure Estimates = $\frac{\text{PHED Exposure (µg /kg ai handled)} \times \text{Rate} \times \text{ATPD (L/day)} \times \text{Absorption Factor}}{\text{bw (70kg)}}$

For dermal exposure, an absorption factor of 16% was used and for inhalation exposure, absorption is expected to be 100%. PHED inhalation unit exposure values were light except for the backpack scenario which was moderate.

[b] MOE = $\frac{\text{NOAEL (mg/kg bw/day)}}{\text{Exposure estimates (mg/kg/day)}}$

[c] Combined MOE = 1/((1/Dermal MOE) + (1/ Inhalation MOE))

Cancer Risk Assessment

It was conservatively estimated that M/L/A could apply Mythic Insecticide 250 days per year given its indoor termiticide use as well as limited outdoor structural and termiticide use in warmer climates. For use on greenhouse ornamentals and fruiting vegetables, handlers are expected to apply approximately 30 days per year.

The cancer risk was calculated for the lifetime of a farmer, custom applicator or PCO applying Mythic Insecticide or Pylon Miticide Insecticide. The absorbed daily dose (ADD) (mg/kg bw/day) was calculated and combined with the treatment frequency (days/year) and the working duration (years) to determine the lifetime absorbed daily dose (LADD) (mg/kg bw/day). The average working duration of a farmer is 40 years (NAFTA, 1999) and 16 years for PCOs based on a study by Carey (1988). The LADD was multiplied by the Q_1* value of 0.0156 $(\text{mg/kg bw/day})^{-1}$ to determine the cancer risk. The cancer risk for all chemical handler scenarios was below the Agency's level of concern (1×10^{-5}) (Table 3.4.2.1.3) except for the backpack M/L/A termiticide scenario. However, given the conservatism associated with the Tier 1 risk assessment defaults and the dermal absorption value, this is not of concern.

Table 3.4.2.1.3: Mixer/Loader/Applicator Dermal and Inhalation Cancer Risk Assessment

Scenario		ADD (mg/kg bw/day)[a]	Treatment Frequency (days/year)	Working Duration (years)	LADD (mg/kg bw/day)[b]	Cancer Risk[c]
Termiticide	Mechanically-pressurized handheld equipment	3.37×10^{-3}	250	16	4.93×10^{-4}	7.7×10^{-6}
	M/L/A Manually-pressurized handwand	1.19×10^{-3}	250	16	1.74×10^{-4}	2.7×10^{-6}
	M/L/A Backback	5.65×10^{-3}	250	16	8.26×10^{-4}	1.3×10^{-5}
	M/L Open Pour Rodding	2.99×10^{-4}	250	16	4.37×10^{-5}	6.8×10^{-7}
Greenhouse Ornamentals	Mechanically-pressurized handheld equipment	8.09×10^{-3}	30	40	3.55×10^{-4}	5.5×10^{-6}
	Manually-pressurized handwand	9.58×10^{-5}	30	40	4.20×10^{-6}	6.5×10^{-8}
	Backpack	2.81×10^{-4}	30	40	1.23×10^{-6}	1.9×10^{-7}
Greenhouse Fruiting Vegetables	Mechanically-pressurized handheld equipment	6.73×10^{-3}	30	40	2.95×10^{-4}	4.6×10^{-6}
	Manually-pressurized handwand	7.96×10^{-5}	30	40	3.49×10^{-6}	5.4×10^{-8}
	Backpack	2.33×10^{-4}	30	40	1.02×10^{-5}	1.6×10^{-7}

[a] Absorbed Daily Dose (ADD) (mg/kg bw/day). To calculate ADD, the dermal and inhalation exposure values from Table 3.4.2.1.2 were summed.

[b] $\text{LADD} = \frac{\text{ADD} \times \text{Treatment Frequency} \times \text{Duration of Exposure (years)}}{365 \text{ days/year} \times \text{Life Expectancy (years)}}$

[c] Cancer Risk = LADD(mg/kg bw/day) × Q_1^*(mg/kg bw/day)$^{-1}$

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Mythic Insecticide

Post-application exposure is expected to be negligible for PCOs using Mythic Insecticide as a termiticide or indoor structural treatment and will not be quantified as part of this assessment.

Pylon Miticide Insecticide

Non-Cancer Exposure and Risk Assessment

There is potential for exposure to workers re-entering greenhouses treated with Pylon Miticide Insecticide when performing activities such as hand harvesting, pinching or tying. The duration of exposure is considered to be long-term and the primary route of exposure is dermal. Inhalation exposure is not of concern as workers are not allowed to re-enter treated greenhouses until 12 hours after application at which time all airborne particles have settled.

Dermal exposure to workers entering treated greenhouses is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients (TCs) and maximum application rates. Maximum application rates were determined based on the approved maximum application rate and a spray volume of 1500L/ha for ornamentals and 1000 L/ha spray volume for vegetables. Transfer coefficients are based on data submitted to the PMRA by the Agricultural Reentry Task Force (ARTF). Transfer coefficients are not available for tomatillo, ground cherry, eggplant or pepino so the TC for other trellised greenhouse crops, such as tomato and pepper, will be used as surrogate data.

Chemical-specific dislodgeable foliar residue data were only submitted for greenhouse ornamentals and as such, a default dislodgeable foliar residue value of 20% of the application rate was used in the exposure assessment for greenhouse vegetables. The dislodgeable foliar residue (DFR) study on greenhouse ornamentals was conducted at a rate that is 62% higher than the label rate. The R^2 values were less than the guideline value of 0.85 and as such, the data were determined to be unsuitable at predicting residue dissipation. However, the peak residues, after correction for the lower Canadian application rate and low field and tank mix recoveries, were used to determine exposure to postapplication workers. For both ornamentals and vegetables, the daily dissipation rate is 0% because it is assumed that residues do not dissipate in greenhouses.

Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 1000 (Table 3.4.2.2.1). The target MOE was not exceeded for greenhouse vegetables and as such, mitigation measures of reducing the application rate and the maximum number of applications per crop cycle are required. When the rate is reduced to a single application of 0.075 g a.i./L per crop cycle, the calculated MOE is acceptable. The calculated MOE for greenhouse ornamentals does not exceed the target MOE of 1000; however, given conservative assumptions in the dermal absorption study, the risk is considered acceptable.

Table 3.4.2.2.1: Non-Cancer Postapplication Margins of Exposure on Greenhouse Ornamentals and Fruiting Vegetables (shaded cells indicate the target MOE is not exceeded)

Crop	Application Rate ($\mu g/cm^2$)	Maximum Number of Applications per Crop Cycle	Transfer Coefficent (cm^2/hr)	Activity	DFR ($\mu g/cm^2$)	Dermal Exposure (mg a.i. / kg bw/day)	Margin of Exposure[c]
Greenhouse Vegetables (tomato, tomatillo, ground cherry, pepper, eggplant, and pepino)	2.28	3	1800	Harvesting, tying	0.456	0.0150[a]	333
	0.75	1		Harvesting, tying	0.150	0.0049[a]	1013
Greenhouse Ornamentals	0.687[b]	3	400	Hand harvesting, pinching, hand pruning	0.687	0.0050	995

[a] Estimated as 20% maximum seasonal application rate × transfer coefficient (cm^2/hour) × 8 hour/day worked × 16% dermal absorption / 70 kg body weight

[b] Based on dislodgeable foliar residue data and adjusted for the maximum Canadian application rate of 0.2744 g a.i./L and a spray volume of 1500 L/ha (412 g a.i./ha).

[c] MOE = NOAEL / Exposure, target MOE = 1000

Reducing the application rate and the number of applications on greenhouse vegetables based on postapplication risk requires a similar change to the greenhouse fruiting vegetables M/L/A exposure and risk assessment presented in Table 3.4.2.1.2. With the lower application rate of 0.75 $\mu g/cm^2$ or 0.075 g a.i./L, the dilution rate for M/L/A is 30 mL product/100L. The previously calculated inhalation MOE and combined MOE for M/L/A using mechanically pressurized handheld equipment were 749 and 905, respectively, which do not exceed the target MOE. The reduced application rate increases the inhalation MOE to 2280 and the combined MOE to 1320 and the cancer risk to 1.5×10^{-6}. The addition of the respiratory protection measures (inhalation hazard) will result in higher MOEs. As such, the equipment restriction for using mechanically pressurized handheld equipment which is placed on greenhouse ornamentals, does not apply to greenhouse vegetables.

Cancer Risk Assessment

To calculate the ADD for greenhouse ornamentals, a time weighted average (TWA) DFR assuming accumulation over time based on 0% daily dissipation was calculated. This value was coupled with days of exposure per year and working duration to determine the LADD (Table 3.4.2.2.2). The ADD for greenhouse vegetables is the dermal exposure (mg/kg bw/day) from the non-cancer assessment when the application rate and number of application per crop cycle are reduced.

Table 3.4.2.2.2: Post-Application Worker Cancer Risk Assessment

Scenario	ADD (mg/kg bw/day) [a]	Treatment Frequency (days/year)	Working Duration (years)	LADD (mg/kg bw/day) [b]	Cancer Risk [c]
Ornamentals	1.26×10^{-2}	30	40	5.51×10^{-4}	8.6×10^{-6}
Vegetables	4.94×10^{-3}	30	40	2.16×10^{-4}	3.4×10^{-6}

[a] Absorbed Daily Dose (ADD) (mg/kg bw/day). To calculate ADD, a time weighted average DFR using the peak residue value from the DFR study was calculated for a period of 30 days over three applications for ornamentals. For greenhouse vegetables, the ADD was calculated based on a single application of 0.075 g a.i./L.

[b] $\text{LADD} = \frac{\text{ADD} \times \text{Treatment Frequency} \times \text{Duration of Exposure (years)}}{365 \text{ days/year} \times \text{Life Expectancy(years)}}$

[c] Cancer Risk = LADD(mg/kg bw/day) × Q_1^*(mg/kg bw/day)$^{-1}$

3.4.3 Residential Exposure and Risk Assessment

A residential postapplication risk assessment was conducted for Mythic Insecticide as a termiticide. Risk estimates were found to be acceptable for this use.

For termiticide treatments, the product is intended to remain in the soil for years of protection against termites so the exposure duration may potentially be 365 days a year. However, based on the submitted indoor air monitoring study, which showed residues of less than level of quantitation (LOQ) over a 30/31 day monitoring period, the residential duration of exposure was reduced to 30 days/year for the cancer risk assessment.

3.4.3.1 Handler Exposure and Risk

Mythic Insecticide is a commercial class insecticide and can only be applied by licensed PCOs. A residential handler risk assessment is not required.

3.4.3.2 Postapplication Exposure and Risk

Termiticide Treatment

Mythic Insecticide is to be applied to soil and buildings to protect against termites. Treatment locations on or around homes include below vertical and horizontal concrete slabs, hollow block foundations or voids, crawl spaces, bath traps, buildings on soil, basements, plenums, structures with adjacent potable water structures. The maximum dilution concentration is 0.25% chlorfenapyr. Application rates vary depending on the location being treated and the application method used.

Non-Cancer Exposure and Risk Assessment

Inhalation is the main route of exposure when Mythic Insecticide is applied subterraneously on or around homes as a termiticide. To determine the indoor air concentration of chlorfenapyr, an indoor air monitoring study was conducted. Soil on the exterior of crawl spaces or basements of

four homes in the US was treated with a single application of 0.5% chlorfenapyr by trenching or rodding application methods. Potential exposure to residents in the homes was determined by using personal sampling pumps containing sorbent tubes sampling at a rate of 1 Lpm in three rooms at various distances from the treatment location. A single sampling pump ran for 6 hours at each of the 6 sampling time periods (pre-treatment, during treatment, immediately after treatment, and then 3, 7, and 30 days after treatment) for a total of 17 samples per house for the entire experiment. A sample was not taken in the basement or crawl space during treatment. Field fortification samples of sorbent tubes spiked at 1× LOQ and 10× LOQ yielded recoveries ranging from 80% to 104%. All samples were less than LOQ (0.5 ng/L or 0.18 µg) and as a result, a value of LOQ was used for risk assessment purposes. The full LOQ rather than ½ LOQ value was used to account for the 2-fold difference between the study and Canadian application rates.

Exposure estimates based on NAFTA inhalation rates (m^3/day) and the study LOQ value of 0.5 ng/L were compared to the toxicological endpoint to obtain the margin of exposure (MOE); the target MOE is 1000 (Table 3.4.3.2.1). The calculated MOEs for the adult, youth, and child age categories all exceeded the target MOE.

Table 3.4.3.2.1: Non-Cancer Post-application Inhalation Margins of Exposure after Termiticide Treatment.

Age Category	Inhalation Rate (m^3/day)[a]	Inhalation Exposure (mg/kg bw/day)	MOE
Adult	13.3	9.50×10^{-5}	1.47×10^{4}
Youth	8.7	1.11×10^{-4}	1.26×10^{4}
Child	4.5	1.50×10^{-4}	9.33×10^{3}

[a] NAFTA, 1999
[b] Inhalation Exposure = Air concentration (mg/L) × Conversion Factor (1000 L/m^3) × Inhalation Rate (m^3/day) (NAFTA)/ Body weight (kg)
[c] MOE = NOAEL / Exposure, target MOE = 1000

Cancer Risk Assessment

The cancer risk from indoor inhalation of chlorfenapyr from soil treatment with Mythic Insecticide is less than the Agency standard of 1×10^{-6} and is considered acceptable (Table 3.4.3.2.2).

Table 3.4.3.2.2: Cancer Risk from Post-application Inhalation Exposure

Age Category	ADD (mg/kg bw/day)[a]	LADD (mg/kg bw/day)[b]	Cancer Risk[c]	Cumulative Lifetime Cancer Risk[d]
Adult	9.50×10^{-5}	6.56×10^{-6}	1.0×10^{-7}	1.3×10^{-7}
Youth	1.11×10^{-4}	7.32×10^{-7}	1.1×10^{-8}	
Child	1.50×10^{-4}	9.86×10^{-7}	1.5×10^{-8}	

[a] Absorbed Daily Dose (ADD) (mg/kg bw/day). To calculate ADD, the exposure values from the non-cancer risk assessment were used.

[b] $\text{LADD} = \frac{\text{ADD} \times \text{Treatment Frequency} \times \text{Duration of Exposure (63 years for adults, 6 years for youth, and 6 years for child)}}{\text{365 days/year} \times \text{Life Expectancy(years)}}$

[c] Cancer Risk = LADD(mg/kg bw/day) × Q_1*(mg/kg bw/day)$^{-1}$

[d] Cumulative Lifetime Cancer Risk = Sum of the individual age category cancer risks

Outdoor Structural

The applicant also requested the use of Mythic Insecticide in outdoor residential areas. Based on the proposed use pattern, where the product will only be applied as spot and crack and crevice treatments where pests enter around doors, windows, eaves, attic vents, and holes in exterior walls where utilities enter, exposure is expected to be negligible.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible due to the areas of application and the label statement that bystanders cannot be present during application unless outfitted in proper personal protective equipment.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for dietary exposure assessment and enforcement in plant products is chlorfenapyr. The data gathering/enforcement analytical method is valid for the quantitation of chlorfenapyr residues in all plant matrices and processed commodities. The residues of chlorfenapyr are stable for 24 months when stored in a freezer between -20°C and -10°C. No residues are expected in animal foodstuff, as there are no feed items derived from the petitioned crops. Greenhouse fruiting vegetables are not expected to be commercially processed.

3.5.2 Dietary Risk Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Acute Dietary Exposure Results and Characterization

An intermediate acute dietary risk assessment was conducted using the following assumptions: 100% crop treated, highest residues from greenhouse trials, no processing factors, no livestock residues and no water residues. A population adjusted dose was determined for the following subpopulations: children <12 years old and females 13-49 years old. The PMRA estimates that the highest exposure and risk estimate is for children 1-2 years old at 21% (0.001046 mg/kg bw/day) of the ARfD.

3.5.2.2 Chronic Dietary Exposure Results and Characterization

A basic chronic risk assessment was conducted using the following assumptions: 100% crop treated, proposed MRLs, no processing factors, no livestock residues and no water residues. The PMRA estimates that chronic dietary exposure to chlorfenapyr is 9 % (0.000451 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 3-5 years old at 21% (0.001025 mg/kg bw/day) of the ADI.

3.5.2.3 Cancer Dietary Exposure Results and Characterization

A refined cancer risk assessment was conducted using the following assumptions: 100% crop treated, United States Food and Drug Administration PDP monitoring residue data, no processing factors, no livestock residues and no water residues. The PMRA estimates that lifetime cancer dietary exposure to chlorfenapyr for the general population is 9×10^{-8}.

3.5.3 Maximum Residue Limits

Table 3.5.3.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Fruiting vegetables: tomato, tomatillo, ground cherry, pepper, eggplant and pepino	2.0

For additional information on Maximum Residue Limits (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodology, field trial data, and the acute, chronic and cancer dietary risk estimates are summarized in Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on the intended use pattern for Mythic Insecticide (indoor and structural uses) and Pylon Miticide Insecticide (greenhouse uses), limited environmental exposure is expected. However, a detailed environmental assessment, including the evaluation of the environmental chemistry and fate of chlorfenapyr was conducted. Chlorfenapyr is a stable and persistent chemical that is immobile in soil. The following paragraphs summarize what happens to chlorfenapyr when it enters the Canadian environment.

Soil, Sediment and Water

Chlorfenapyr is stable to hydrolysis at environmentally relevant pH. Photolysis on soil is not a significant route of transformation (half-lives of 67 and 77 days for the ^{14}C-phenyl and ^{14}C-pyrolle labels, respectively). Two minor transformation products (TP) were identified as CL 325195 and CL 303268, both at approximately 5% of the Applied Radioactivity (AR). Several other minor soil phototransformation products were formed, however, these were not identified, and none accounted for more than 3% of the AR. Photolysis in water is relatively faster than on soil, with half lives of 4.2, 8 and 22 days at pH 5, pH 7 and pH 9, respectively, and the formation of a major TP: CL 357806 (an isomer of the parent compound) at 53-66% of the AR. So, although not rapid, aquatic phototransformation may be an important transformation route for chlorfenapyr in the photic zone of a water body.

Chlorfenapyr is persistent in soil. Laboratory studies indicate that slow aerobic biotransformation is a route of chlorfenapyr transformation with half-lives ranging from 239 to 3670 days. The 80th percentile value is 1678 days. Four minor transformation products were identified: CL 312094, CL 303267, CL 303268, and CL 325295, ranging in concentration from 1 to approximately 8% of the AR.

Chlorfenapyr is persistent in water/sediment systems. Laboratory studies indicate that aquatic biotransformation is slow, with a whole system half-life of 218 - 418 days for aerobic and 202 days for anaerobic conditions. Chlorfenapyr does not remain in the water layers. It moves from the water phase into the sediment phase, and then persists in the sediment phase (anaerobic biotransformation half-lives of 196 days in sediment). The major transformation product is CL 312094 under both aerobic and anaerobic conditions (24.5% of the AR on Day 365 for anaerobic).

Chlorfenapyr does not have a measureable pKa value as there are no ionisable groups on the molecule. This means that the compound will be present in its non-dissociated form at environmentally relevant pH; and due to its neutral charge, pH levels should not affect the mobility of chlorfenapyr in soil.

Chlorfenapyr is immobile in soil based on adsorptive characteristics derived from laboratory batch equilibrium studies, and according to the mobility classification scheme of McCall (McCall, 1981). The transformation product CL 312094 displays slight to low mobility in soil and the transformation product 303267 displays high mobility in soil. According to HPLC analysis, the transformation product 325195 displays low mobility in soil.

Air

The low vapour pressure (5.4×10^{-6} Pa at 25 °C) and Henry's law constant (8.22×10^{-6} atm-m^3-mol^{-1}) indicate that chlorfenapyr is non-volatile under field conditions and from water and moist soil surfaces. Therefore, chlorfenapyr residues are not expected to volatilize into the atmosphere, nor is long-range aerial transport expected as a result of volatilization.

Biota

Although the *n*-octanol-water partition coefficient indicates that there may be a potential for bioconcentration in organisms (log K_{ow} 5.24 at pH 7), results from laboratory studies in fish show a steady state BCF in whole fish of 97 + 14.2 mL/g, followed by depuration within 3-4 days, indicating that bioaccumulation is not a concern for chlorfenapyr.

Data on the environmental fate and behaviour of chlorfenapyr in the terrestrial and aquatic environment are summarized in Appendix I, Table 12 and Table 13.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are calculated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 2 for beneficial arthropods and LOC = 1 for all remaining non-target organisms). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then

a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

In the case of chlorfenapyr, the non-target organisms considered in the risk assessment included pollinators and beneficial arthropods (i.e. predatory and parasitic insects), as these groups of organisms could realistically expect chlorfenapyr exposure where Pylon Miticide Insecticide is being used in greenhouses. The screening level estimated environmental concentration (EECs) were calculated using the maximum application rate and the accompanying maximum water spray volumes per unit area to derive a conservative EEC. However, smaller spray volumes per unit area will result in lower application rates and will translate into lower EEC values. As such, for the refined assessment, the maximum label rate was modified to reflect the EEC that would result from the smallest possible efficacious water spray volume (350 L/ha for small bedding plants to represent ornamentals and 285 L/ha for small tomatoes to represent fruiting vegetables). As well, the minimum application rates, along with the minimum water spray volumes were also investigated. This was done in order to further bracket the description of potential risk to pollinators and beneficial arthropods.

Risks of Chlorfenapyr Exposure (Pylon Miticide Insecticide) to Non-Target Organisms

Non-target terrestrial invertebrates such as pollinators and beneficial arthropods, may be exposed to Pylon Miticide Insecticide through direct application, contact with treated plant material, or from ingestion of contaminated pollen after foliar application in greenhouses. The risk of chlorfenapyr exposure to these terrestrial invertebrates was based on the use pattern for the end-use product and the evaluation of acute contact and acute oral ecotoxicity data.

Pollinators

Chlorfenapyr may pose a risk to honeybees. The 96-hour LD_{50} values were 0.33 µg a.i./bee and 1.0 µg a.i./bee for acute contact and acute oral exposure, respectively. Thus, chlorfenapyr is classified as highly toxic to the honey bee via the contact and oral routes of exposure, according to the Atkins classification system (Atkins, 1981).

At the proposed maximum cumulative application rate and the maximum single application rate, risk quotient values were greater than the level of concern on a contact basis (screening level RQs of 1.3–2.8). On an oral basis, the risk quotient values were less than the level of concern (screening level RQs of 0.4–0.91, Appendix I, Table 14).

During greenhouse application, there is a great variation in the volumes of spray solution utilized for a given area. In order to further bracket the description of potential risk found in greenhouses, the risk quotients were calculated for small bedding plants (representing ornamentals) and small tomatoes (representing fruiting vegetables) using the minimum required spray volumes. These were chosen to provide the lower range of potential EEC values. When

one uses both the maximum and minimum application rate (in combination with the minimum spray volume) to give the smallest possible, yet realistic EEC value (i.e. a refined EEC value), the LOC is not exceeded for either crop group (ornamentals or fruiting vegetables) for honeybees. The refined RQ values range from 0.028–0.78 (Appendix I, Table 15).

This calculation was conducted using the minimum spray volume in order to bracket the risk information by providing the range of RQ values that result from lower use rates. As maximum application rates and maximum water spray volumes can be used in standard greenhouse practice, the risk to honeybees as a result of chlorfenapyr exposure cannot be entirely ruled out.

Beneficial Arthropods

Chlorfenapyr may pose a risk to beneficial arthropods. At the concentrations used in the ecotoxicity limit tests (which were comparable to the upper range of the proposed maximum single application rate), there was extensive mortality due to test substance exposure (i.e. mortality was 33–100% after 24 hours and 99–100% after 96 hours). Due to the extensive mortality, it was not possible to quantify the sublethal effects, nor adverse effects on reproduction. As each of the studies were conducted as limit tests, the results are expressed as LR_{50} < test substance concentration. The 96-hour LR_{50} values ranged from < 262 to < 265 g a.i./ha for the predatory mite and parasitic wasp, < 217 g a.i./ha for the predatory bug, and < 199 to < 545 g a.i./ha for predatory beetles. Because the LR_{50} values are expressed with a " < " sign, the resulting RQ values are expressed with a " > " sign. The screening level risk quotient values were greater than the level of concern (LOC = 2) for all representatives of the beneficial arthropod species (Appendix I, Table 16).

When one uses the maximum application rate in combination with the minimum spray volume to calculate refined EEC values, the LOC is still definitively exceeded for ornamentals (i.e. small bedding plants) for all the beneficial arthropods except one, the carabid beetle, where RQ > 0.72 (Appendix I, Table 17). When one uses the minimum application rate in combination with the minimum spray volume, the LOC values range from RQ > 0.08 to RQ > 0.66 for the various beneficial arthropods (this includes both maximum and minimum application rates along with the minimum spray volume). However, because all refined RQ values are expressed with a " > " sign (resulting from the way in which the ecotoxicity tests were carried out: limit tests with effects observed at the one concentration tested), this means that the quantification of the excess above the LOC value is not entirely certain. This further means that even where the LOC values are below one, harmful effects on beneficial arthropods resulting from chlorfenapyr exposure cannot entirely be ruled out. Furthermore, it is standard greenhouse practice to use large spray volumes, along with the maximum application rate (to ensure product efficacy), and at the higher application rates, the level of concern is definitely exceeded.

Chlorfenapyr exposure at the application rates tested, which are comparable to actual use rates provided on the Pylon Miticide Insecticide product label, show the potential for risk to pollinators (i.e. honey bees) as well as foliage-dwelling and soil-dwelling beneficial arthropods. It was not possible to refine the expected risk to below the level of concern with any degree of certainty. Thus, in order to protect beneficial insect populations in greenhouses, mitigative label statements are required. These statements should note the toxicity of chlorfenapyr to beneficial

arthropods, as well as cautioning users about the potential effects of using chlorfenapyr when beneficial arthropods are inhabiting the greenhouse at time of spraying.

Non-target Aquatic Organisms

The exposure of non-target aquatic organisms to chlorfenapyr as a result of the use of Pylon Miticide Insecticide is expected to be minimal. This product is not being proposed for aquatic uses nor for outdoor agricultural uses. An assessment of the adverse effects of Pylon Miticide Insecticide on non-target aquatic organisms was not required due to the use pattern being restricted to use in greenhouses.

Risks of Chlorfenapyr Exposure (Mythic Insecticide) to Non-Target Organisms

The exposure of non-target organisms (both aquatic and terrestrial) to chlorfenapyr as a result of the use of Mythic Insecticide is expected to be minimal. This product is being proposed for indoor use, and outdoor use is limited to application of exterior structures. An assessment of the adverse effects of Mythic Insecticide on non-target organisms was not required due to the use pattern as a crack and crevice treatment.

5.0 Value

5.1 Effectiveness Against Pests

Pylon Miticide Insecticide

Twenty-one trials were conducted against various mite species. For greenhouse ornamentals, 20-41 ml product/100 L of water (4.8- 9.8 g a.i./100 L) were supported for control of two-spotted spider mite. For the listed greenhouse fruiting vegetables, 20-30 ml product/100 L of water (4.8-7.2 g a.i./100 L) were supported for suppression of two-spotted spider mite.

Twenty-four trials were conducted against various lepidopteran species. For greenhouse ornamentals, 30-50 ml product /100 L of water (7.2 - 12 g a.i./100 L) were supported for control of cabbage looper and soybean looper. For greenhouse fruiting vegetables, 30 ml product/100 L of water (7.2 g a.i./100 L) were supported for suppression of tomato hornworm, tobacco budworm, cabbage looper and alfalfa looper.

Nine trials were conducted against Western flower thrips and four trials against melon thrips. For greenhouse ornamentals, 78-156 ml product/100 L of water (18.7-37.4 g a.i./100 L) were supported for control of Western flower thrips.

Eight laboratory bioassays and greenhouse trials were submitted to support the claim of control of foliar nematodes on greenhouse ornamentals. Overall, the efficacy trials demonstrated that Pylon Miticide Insecticide effectively reduced foliar nematodes under severe infestation in greenhouse conditions. The claim for control of foliar nematodes (*Aphelenchoides* spp.) on greenhouse ornamentals was supported at concentrations of 41-78 ml product/100 L of water.

Initial application is to be made at first signs of plant damage by nematodes, followed by a second application after 7-14 days. A third application can be made at 4-6 weeks following the initial application if plant damage or nematodes are detected. The higher rate is to be used under severe pest pressure.

Mythic Insecticide

Twenty-two efficacy trials were used in the assessment of the performance of Mythic Insecticide. Most of these trials were conducted under laboratory conditions except the termite trials where all or part of the trial was conducted in a field or operational situation. The efficacy data consisted of three trials against seven species of ants, three trials against four species of spiders, two trials against European earwig, three trials on subterranean termites and one trial each against house flies, paper wasps, Asian lady beetles, boxelder bugs, centipedes, house crickets, pillbugs and silverfish,. Overall, the efficacy trials demonstrated that Mythic Insecticide killed ants at 0.125-0.25% chlorfenapyr, Asian ladybird beetles, boxelder bugs, centipedes, European earwigs, house crickets, paper wasps, pillbugs, and spiders at 0.25% chlorfenapyr, and house flies at 0.5% chlorfenapyr. The efficacy data also supported the use of Mythic Insecticide to control subterranean termites at concentrations of 0.125 to 0.25% when applied as pre-construction and post-construction treatments. It is recommended that Mythic Insecticide be applied directly to the pest for it to be killed.

5.2 Non-Safety Adverse effects

Phytotoxicity to Host Plants (Pylon Miticide Insecticide):

The efficacy trials described above either made no mention of phytotoxicity, or specifically mentioned that no phytotoxicity had been observed. Fifteen trials on ornamentals were conducted specifically to evaluate phytotoxicity. It was observed that concentrations within the proposed range did not cause phytotoxicity to African daisy, African violet, aster, azalea, begonia, chrysanthemum, croton, gardenia, lisianthus, miniature rose or verbena and therefore the "no unacceptable injury" claim is supported for these ornamental species.

Structural Uses (Mythic Insecticide):

Non-safety adverse effects were not identified in any of the provided information. The following statement is located on the label: "Treat a small and inconspicuous area of surface to be treated to determine if staining or other damage will occur prior to treating an entire area."

5.3 Sustainability

5.3.1 Survey of Alternatives

Pylon Miticide Insecticide

Pyrethrins and potassium salts of fatty acids are registered for control of mites in greenhouses.

Spinosad, chlorantraniliprole and lambda-cyhalothrin are registered for control of cabbage looper on greenhouse fruiting vegetables.

No alternatives are registered for control of foliar nematodes on greenhouse ornamentals or tomato hornworm or tobacco budworm on greenhouse fruiting vegetables.

Mythic Insecticide

Pyrethrins and pyrethroids (MOA 3A) constitute most of the active ingredients currently registered to kill the pests listed on the Mythic Insecticide label. Organophosphates (MOA 1A) and carbamates (MOA 1A) are also used against the pests listed on the Mythic Insecticide label; however, several of these active ingredients are in the process of being phased out (for example, azamethiphos, bendiocarb) or their use patterns have been amended, limiting their use to specific sites or to specific application methods (for example, dichlorvos, propetamphos). Other active ingredients registered for use in structural sites are currently under re-evaluation (for example, malathion, pyrethroids). For some pests (for example, house flies, ants), there are other registered active ingredients belonging to a different MOA (for example, abamectin, hydramethylnon, imidacloprid). A microbial active ingredient (i.e. *Beauvaria bassiana* strain HF 23) and a pheromone (i.e. (z)-9-tricosene) are registered for use against house flies. Although there are other active ingredients registered against subterranean termites, permethrin is the only registered active ingredient being used as a soil-applied termiticide to control subterranean termites in similar use locations (i.e. pre and post construction). Other active ingredients registered for use against subterranean termites include boracic acid, borax, silicon dioxide and silica gel. Fumigants are also registered against some of the structural pests but the use pattern is not comparable to that of Mythic Insecticide. For further information, refer to Appendix I, Table 19.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Pylon Miticide Insecticide is compatible with current pest management practices. Growers are familiar with the monitoring techniques to determine if and when applications are needed. Mythic Insecticide is compatible with current pest management practices. Users are familiar with the monitoring techniques to determine if and when applications are needed.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

In Canada, no active ingredients are currently registered with the same mode of action as chlorfenapyr. Therefore, the use of chlorfenapyr in rotation with other insecticides belonging to different MOA classes would contribute to resistance management.

The Pylon Miticide Insecticide and Mythic Insecticide labels include resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, Chlorfenapyr and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Chlorfenapyr does not meet all the Track 1 criteria, nor does it form any transformation products that meet all Track 1 criteria, and therefore chlorfenapyr is not considered a Track 1 substance. See Appendix I, Table 18 for comparison with Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list

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5 DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade chlorfenapyr and the end use product Pylon Miticide Insecticide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

- The end-use product Mythic Insecticide does not contain any formulants of health or environmental concern identified in the *Canada Gazette*. However, it contains 1,2 benzisothiazolin-3-one at 0.035% as a preservative. The presence of this preservative must appear on the front page of the product label.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for chlorfenapyr is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of genotoxicity, and no evidence of carcinogenicity in mice after longer-term dosing. In rats, however, an increased incidence of haematopoietic system tumours was observed in males. In short-term and chronic studies on laboratory animals, the primary effects included decreases in bodyweight, bodyweight gain and food consumption, and mortality, as well as effects on the nervous system (vacuolation of the brain and spinal cord) and the liver. Mortality was also observed following inhalation exposures, and occurred at lower doses compared to when administered orally. There was evidence of increased susceptibility of the young in reproduction and developmental toxicity studies. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders, applicators handling Mythic Insecticide and Pylon Miticide Insecticide and workers re-entering treated greenhouses are not expected to be exposed to levels of chlorfenapryr that will result in an unacceptable risk when the Mythic Insecticide and Pylon Miticide Insecticide are used according to label directions. The personal protective equipment on the product label is adequate to protect workers when coveralls with a long-sleeved shirt, long pants, shoes and socks with chemical resistant gloves are worn for Pylon Miticide Insecticide and

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7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

long-sleeved shirt, long pants, shoes and socks with chemical resistant gloves are worn for Mythic Insecticide. Further to this, based on the acute inhalation hazards, all workers will be required to wear a respirator during mixing/loading of Mythic Insecticide and during mixing/loading and application of Pylon Miticide Insecticide. Workers cannot mix, load and apply more than 80L of Mythic Insecticide with mechanically pressurized handheld equipment. Pylon Miticide Insecticide cannot be applied to greenhouse ornamentals using mechanically pressurized handheld equipment due to unacceptable risks to workers. The maximum application rate for greenhouse vegetables must be reduced to 0.075 g a.i./L assuming a maximum spray volume of 1000 L/ha and only one application per crop cycle.

Residential exposure and risks to individuals contacting treated areas is acceptable when Mythic Insecticide is used according to label directions as a termiticide and outdoor structural insecticide.

The nature of the residue in citrus fruits, cotton, lettuce, potato and tomato is adequately understood. The residue definition in plants, for enforcement and dietary exposure assessment purposes, is chlorfenapyr. The proposed use of chlorfenapyr on fruiting vegetables does not constitute an unacceptable acute or chronic dietary risk to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend that the following maximum residue limits be specified for residues of chlorfenapyr:

- 2.0 ppm in and on fruiting vegetables: tomato, tomatillo, ground cherry, pepper, eggplant and pepino

7.2 Environmental Risk

Chlorfenapyr is a stable and persistent chemical that is immobile in soil. It is toxic to pollinators and beneficial arthropods. Environmental label statements are required for the protection of these sensitive non-target organisms.

7.3 Value

Pylon Miticide Insecticide has value in controlling two-spotted spider mite, listed Lepidopteran pests, foliar nematodes and Western flower thrips in greenhouse ornamentals and suppressing two-spotted spider mite, listed Lepidopteran pests, Western flower thrips and onion thrips on greenhouse fruiting vegetables.

Mythic Insecticide has value in killing the following pests: ants, Asian ladybird, boxelder bugs, centipedes, European earwigs, house crickets, house flies, paper wasps, pillbugs and silverfish and spiders on the exterior of various structures. In addition, value information supported the use of Mythic Insecticide both pre-construction and post-construction for the control of subterranean termites.

7.4 Unsupported Uses

Pylon Miticide Insecticide

Pylon Miticide Insecticide is not supported for the following uses on greenhouse ornamentals:

1. For use against citrus budmite because this pest is not found in Canada; and
2. For use against beet armyworm because this is not a greenhouse pest in Canada.

Pylon Miticide Insecticide is not supported for the following uses on greenhouse fruiting vegetables:

1. For use against several species of armyworms (i.e. beet, southern, fall, yellowstriped) because these are not greenhouse pests in Canada;
2. For use against melon thrips because this pest is not found in Canada; and
3. For use against tomato pinworm, tomato fruitworm, Western flower thrips and onion thrips because the concentrations required for efficacy exceed what is acceptable in the overall risk assessment.

Mythic Insecticide

The use of Mythic Insecticide is not supported for bark scorpions because these are not pests in Canada.

Several pests (i.e. darkling beetles, confused flour beetles, saw-toothed grain beetles, bed bugs, cockroaches) were not supported for the exterior of structures because these are primarily indoor pests.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Chlorfenapyr Technical Insecticide, Mythic Insecticide and Pylon Miticide Insecticide, containing the technical grade active ingredient chlorfenapyr. Mythic Insecticide is intended for use as in limited applications to the exterior of buildings against various pests and as pre-construction and post-construction termiticide. Pylon Miticide Insecticide is intended for use on greenhouse ornamentals and greenhouse fruiting vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

Acronym	Definition
♂	male
♀	female
µg	microgram(s)
µm	micrometres
a.i.	active ingredient
A/G	albumin/globulin ratio
ADD	absorbed daily dose
ADI	acceptable daily intake
ADP	adenosine diphosphate
ALP	alkaline phosphatase
appl.	application
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
atm	atmosphere(s)
ATP	adenosine triphosphate
ATPD	area treated per day
BAF	bioaccumulation factor
BBCH	Biologische Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
CHL	Chinese hamster lung
CHO	Chinese hamster ovary
CK	creatine kinase
cm	centimetre(s)
DACO	data code
DAT	day(s) after treatment
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT50	dissipation time 50% (the time required to observe a 50% decline in concentration)
ECD	electron capture detector
EEC	estimated environmental concentration
EP	End-use product
EPA	Environmental Protection Agency
F_1	first filial generation

Acronym	Definition
F_2	second generation
fc	food consumption
g	gram(s)
GAP	good agricultural practice
GC	gas chromatography
GD	gestation day
GI	gastrointestinal
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene
Hgb	Hemoglobin
HGPRT	hypoxanthine guanine phosphoribosyl transferase
HPLC	high pressure liquid chromatography
hr	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	n-octanol–water partition coefficient
L	liter(s)
LADD	lifetime absorbed daily dose
LC_{50}	lethal concentration 50%
LD	lethal dose
LD_{50}	lethal dose 50%
LLMV	lowest limit of method validation
LOAEC	Lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
Lpm	litres per minute
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting
M	male
m	metre(s)
M/L/A	mixer , loader and applicator
MAS	mean average score
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MMAD	mass median aerodynamic diameter
MOA	mode of action
MOE	margin of exposure
mol	mole(s)
MRL	maximum residue limit
MS/MS	tandem mass spectrometry
N/A	not applicable

Acronym	Definition
NA	nutrient agar
NAFTA	North American Free Trade Agreement
ng	nanogram(s)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NZW	New Zealand white
P	parental generation
Pa	pascal(s)
PBI	plant-back interval
PCO	pest control operator
PES	post extraction solids
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PM	afternoon or evening
PMRA	Pest Management Regulatory Agency
PND	post-natal days
PPE	personal protective equipment
ppm	parts per million
Q_1*	cancer potency factor
R^2	coefficient of determination
RQ	risk quotient
RTI	retreatment interval
SFO	simple first order
SOP	standard operating procedure
TC	transfer coefficient
TGAI	technical grade active ingredient
TP	transformation products
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TWA	time weighted average
UFDB	database uncertainty
US	United States
USC	use site category
UV	ultraviolet
WBC	white blood cell
wk	week(s)
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Soil	M2201	Parent (CL303630)	GC-ECD	0.01 ppm		1859807
Plant	M2427	Chlorfenapyr	GC-ECD – quantitation GC-MSD or GC-NPD - confirmation	0.05 ppm	All plant commodities except: (see below)	PMRA # 1859971 1859975 1859803
				0.01	Tomato juice, potato, potato processed commodities	

Table 2 Toxicity Profile of Mythic Insecticide and Pylon Miticide Insecticide Containing Chlorfenapyr

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague Dawley rats PMRA #1859952	LD_{50} = 560 mg/kg bw Moderate toxicity
Acute dermal toxicity NZW rabbits PMRA #1859954	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague Dawley rats PMRA #1859956	LC_{50} = 0.571 mg/L (♂) LC_{50} > 2.43 mg/L (♀) Note: MMAD mean 4.5 µm (range 4.0-4.9 µm); 34-49% particle ≤ 4 µm Increased one level due to issues with particle size, and close proximity of male LC_{50} to moderate toxicity classification range. Moderate toxicity

Study Type/Animal/PMRA #	Study Results
Dermal irritation NZW rabbits PMRA #1859960	MIS = 0.5 (1 hr), MAS = 0.06 Minimally irritating
Eye irritation NZW rabbits PMRA #1859958	MIS = 3 (1 hr), MAS = 0 Non-irritating
Dermal sensitization (Buehler test) Dunkin Hartley guinea pigs PMRA #1859961	Non-sensitizer

Table 3 Toxicity Profile of Technical Chlorfenapyr

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague Dawley rats PMRA #1859724	LD_{50} = 441 mg/kg bw High toxicity
Acute oral toxicity CD-1 Mice PMRA #1859726	LD_{50} = 45 mg/kg bw High Toxicity
Acute dermal toxicity NZW Rabbits PMRA #1859727	LD_{50} > 2000 mg/kg bw Low Toxicity

Study Type/Animal/PMRA #	Study Results
Acute inhalation toxicity (whole body) Sprague Dawley rats PMRA #1859728	LC_{50} = 0.83 mg/L Note: MMAD mean 7.1 µm (range 5.9-8.1 µm); 30-40% particle < 5 µm Increased one hazard level due to particle size issue Moderate Toxicity
Dermal irritation NZW Rabbits PMRA #1859733	MIS = 1 (1 hr), MAS = 0 Non-irritating
Dermal irritation NZW Rabbits PMRA #1859734	MIS = 0, MAS = 0 Non-irritating
Eye irritation NZW Rabbits PMRA #1859729	MIS = 13.7 (24 hr), MAS = 7.7 Increased one hazard level due to persistence Mild Irritation
Eye irritation NZW Rabbits PMRA #1859732	MIS = 15.7 (24 hr), MAS = 10.1 Increased one hazard level due to persistence Mild Irritation
Skin sensitization (Maximization Test) Hartley Guinea Pigs PMRA #1859735	Non-sensitizer
28-day dietary toxicity CD-1 Mice PMRA #1859756	A NOAEL and LOAEL were not established as this was a dose range-finding / supplemental study. Adverse effects noted at ≥ 44/58 mg/kg bw/day (240 ppm) included: ↑ mortality (during first 7 days of the study] (♂); ↑ liver wt, ↑ hepatocellular hypertrophy (♀).

Study Type/Animal/PMRA #	Study Results
90-day dietary toxicity CD-1 Mice PMRA #1859740	NOAEL= 7.1/9.2 mg/kg bw/day (40 ppm) LOAEL = 15/19 mg/kg bw/day (80 ppm) Based on ↑ lymphocytes, ↓ neutrophil counts, ↑ hepatic parenchymal hypertrophy (♂).
28-day dietary toxicity Sprague-Dawley rats PMRA #1859755	A NOAEL and LOAEL were not established as this was a dose range-finding study. Adverse effects noted at ≥ 68/75 mg/kg bw/day (600 ppm) included: ↓ bwg and fc, ↑ liver wt
90-day dietary toxicity Sprague-Dawley rats PMRA #1859737	NOAEL = 22/26 mg/kg bw/day (300 ppm) LOAEL = 45/52 mg/kg bw/day (600 ppm) Based on ↓ bw and bwg, ↑ ALP, spongiform myelopathy in brain and spinal cord, testicular atrophy (♂); ↓ Hgb, ↑ ovarian/uterine wt (♀)
90-day dietary toxicity Beagle dog PMRA #1859757	NOAEL = 3.9/4.5 mg/kg bw/day (120 ppm) LOAEL = 6.0/5.8 mg/kg bw/day (240 ppm) Based on emaciation during 1st month, bw loss during wk 0-2, ↓ bw and fc during 1st month (when dose level was 300/240 ppm), ↓ bwg overall (due to bw loss in wk 0-2); emesis during 1st wk (1♀) (An analysis at each of the sub-dosing periods (300, 240, 200 ppm) suggests that the above effects are most likely a result of reduced palatability of the test diet and not directly attributed to test article toxicity)
12-month dietary toxicity Beagle dog PMRA #1859754	NOAEL = 2.1/2.3 mg/kg bw/day (60 ppm) LOAEL = 4.0/4.5 mg/kg bw/day (120 ppm) Based on ↑ number and size of lymphoid follicles in the stomach.
28-day dermal toxicity Wistar rat PMRA #1859765	NOAEL = 206 mg/kg bw/day LOAEL = 835 mg/kg bw/day Based on anogenital region smeared with urine, ↓ albumin, ↑ globulin, ↑ triglycerides, ↑ phosphorous, ↑ cholesterol, ↑ BUN, ↑ liver wt; piloerection, ↓ rearing (♀)
28-day dermal toxicity NZW rabbit PMRA #1859761	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Adverse effects at ≥ 400 mg/kg bw/day included: ↑ cholesterol, ↑ liver wt, cytoplasmic vacuolation of hepatocytes; ↑ CK, discolouration of the liver (♀)

Study Type/Animal/PMRA #	Study Results
90-day inhalation toxicity (nose-only) Wistar rats PMRA #1859768	NOAEC = 5 mg/m^3 (1.4 mg/kg bw/day) LOAEC = 20 mg/m^3 (5.4 mg/kg bw/day) Based on ↑ motor activity;↑ rearing, ↓ testes wt, ↓ epididymal wt (♂) Increased mortality in males was noted at the next higher dose level (40 mg/m^3; 11 mg/kg bw/day). Effects following a 28-day recovery period were noted at 40 mg/m^3 (11 mg/kg bw/day), and included ↓ WBC.
18-month dietary oncogenicity CD-1 Mice PMRA #1859774	NOAEL = 2.8/3.7 mg/kg bw/day (20 ppm) LOAEL = 17/22 mg/kg bw/day (120 ppm) Based on ↓ fc throughout the study, ↑ incidence of vacuolation of the white matter of the brain (corpus callosum, tapetum, hippocampus and cerebellum) and spinal cord (observed at both 52 and 80 wks); ↓ bw and bwg (♀) No evidence of carcinogenicity
24-month dietary chronic toxicity/oncogenicity Sprague-Dawley rats PMRA #1859772	NOAEL = 2.9/3.6 mg/kg bw/day (60 ppm) LOAEL = 15/19 mg/kg bw/day (300 ppm) Based on ↓ bw and bwg, ↑ globulin, ↓ A/G ratio, ↑ liver wt and hepatocellular enlargement; ↓ food conversion efficiency,↑ cholesterol (♀) Evidence of carcinogenicity (histiocytic sarcomas and lymphocytic lymphomas in males)
Range-finding one generation reproductive toxicity (dietary) Sprague Dawley Rat PMRA #1859777	A NOAEL and LOAEL were not established as this was a dose range-finding study. Adverse effects noted in parental animals at ≥ 20/24 mg/kg bw/day (300 ppm) included ↓ bw and bwg during premating (♀). Adverse effects noted in offspring at ≥ 20/24 mg/kg bw/day (300 ppm) included ↓ viability index. An increased incidence of pup mortality during PND 0-4 was observed at the next higher dose level (41/49 mg/kg bw/day) There were no adverse effects noted on reproductive toxicity parameters at any of the doses tested.

Study Type/Animal/PMRA #	Study Results
Multigeneration reproductive toxicity (dietary) Sprague Dawley Rat PMRA #1859778	Parental toxicity: NOAEL (♂) = 4.5 mg/kg bw/day (60 ppm) LOAEL (♂) = 22 mg/kg bw/day (300 ppm) Based on ↓bw and bwg during premating (P♂) NOAEL (♀) = 25 mg/kg bw/day (300 ppm) LOAEL (♀) = 48 mg/kg bw/day (600 ppm) Based on ↓ fc during premating (P) and GD 0-7 (P), ↓ bwg during premating (P and F_1), gestation (F_1) and lactation (P), ↓ bw on GD 7 and 14 (P) and LD 14 and 21 (P). Offspring toxicity: NOAEL = 4.5/5.0 mg/kg bw/day (60 ppm) LOAEL = 22/25 mg/kg bw/day (300 ppm) Based on ↓ pup wt during lactation (F_1& F_2). An increased incidence of still births and pup mortality during PND 0-4 was noted in F_2pups at the next higher dose level (44/48 mg/kg bw/day). Reproductive toxicity: NOAEL = 44/48 mg/kg bw/day (600 ppm) LOAEL not established as there were no effects on measured reproductive parameters. Evidence of sensitivity of the young
Range-finding developmental toxicity (gavage) Sprague-Dawley Rats PMRA #1859783	A NOAEL and LOAEL were not established as this was a dose range-finding study. Adverse effects noted in maternal animals at ≥ 160 mg/kg bw/day included slight ↓ bwg (GD 6-9), slight ↓ fc (GD 6-12). There were no adverse effects noted in the developing fetus at any dose tested.

Study Type/Animal/PMRA #	Study Results
Developmental toxicity (gavage) Sprague-Dawley Rats PMRA #1859783	Maternal toxicity NOAEL = 25 mg/kg bw/day LOAEL = 75 mg/kg bw/day Based on ↓ fc Developmental toxicity NOAEL = 75 mg/kg bw/day LOAEL = 225 mg/kg bw/day Based on ↑ incidence of unossified sternebrae (but overall combined incidence of unossified and/or incompletely ossified sternebrae was comparable to controls), slight ↑ rib pairs and thoracic ossification sites, slight ↓ lumbar ossification sites No evidence of malformations No evidence of sensitivity of the young
Range-finding developmental toxicity (gavage) NZW Rabbits PMRA #1859784	A NOAEL and LOAEL were not established as this was a dose range-finding study. Adverse effects noted in maternal animals at ≥ 50 mg/kg bw/day included mortality (following a single dose), excessive salivation and impaired righting reflex. At the highest dose level (100 mg/kg bw/day), abortion was noted in 1 dam. Adverse developmental effects noted at ≥ 50 mg/kg bw/day included ↓ fetal bw. At the highest dose level (100 mg/kg bw/day), abortion was noted in 1 dam.
Developmental toxicity (gavage) NZW Rabbits PMRA #1859784	Maternal toxicity NOAEL = 15 mg/kg bw/day LOAEL = 30 mg/kg bw/day Based on ↓ fetuses/dam, ↑ early resorptions, ↑ post-implantation loss Developmental toxicity NOAEL =15 mg/kg bw/day LOAEL = 30 mg/kg bw/day Based on ↓ fetuses/dam, ↑ early resorptions, ↑ post-implantation loss No evidence of malformations Evidence of sensitivity of the young

Study Type/Animal/PMRA #	Study Results
Gene mutations in bacteria (Ames test) *S. typhimurium* strains: TA98, TA100, TA1535, TA1537 and TA1538; WP2 uvrA PMRA #1859785	Negative
Gene mutations in mammalian cells *in vitro* CHO cells PMRA #1859790	Negative
Gene mutations in mammalian cells *in vitro* CHO/HGPRT cells PMRA #1859792	Negative
Gene mutations in mammalian cells *in vitro* CHL cells PMRA #1859793	Negative
Micronucleus assay *in vivo* Mouse bone marrow PMRA #1859794	Negative
Unscheduled DNA synthesis Primary rat hepatocytes PMRA #1859795	Negative
Acute neurotoxicity (gavage) Sprague-Dawley rats PMRA #1859780	NOAEL = 45 mg/kg bw LOAEL = 90 mg/kg bw Based on ↑ incidence of animals lying flattened in the cage; ↓ motor activity, lethargy, altered tail pinch response (♂).

Study Type/Animal/PMRA #	Study Results
12-month dietary neurotoxicity Sprague-Dawley rats PMRA #1859744	NOAEL = 2.6/3.4 mg/kg bw/day (60 ppm) LOAEL = 14/18 mg/kg bw/day (300 ppm) Based on ↓ bw, bwg, food conversion efficiency and water consumption; ↑ incidence myelin sheath swelling, vacuolar myelinopathy and vacuolation in central and peripheral nervous tissue (♂). Recovery: Effects following a 16-week recovery period were noted at 28/37 mg/kg bw/day (600 ppm), and included single incidences of vacuolation in the corpus callosum and cerebral peduncle (♂).
Developmental neurotoxicity (gavage) Wistar rats PMRA #1859782	Maternal Toxicity NOAEL = 15 mg/kg bw/day LOAEL not established since there were no treatment-related effects at any dose tested. Offspring Toxicity NOAEL = 5.0 mg/kg bw/day LOAEL = 10 mg/kg bw/day Based on ↑ mortality PND 0-4, ↓ motor activity at PND 13; ↓ mean # of animals reaching criteria in M-maze 're-learning' task at PND 23 and failure to demonstrate improvement in time to complete M-maze 're-learning' task at PND 60 (♂). Evidence of sensitivity of the young
Metabolism Sprague Dawley rat PMRA #1859796	Multiple metabolism investigations were conducted with ^{14}C-chlorfenapyr (labeled either at C2 of the pyrrole ring or uniformly labeled in the phenyl ring), including a single oral low dose (20 mg/kg bw), a single oral high dose (200 mg/kg bw), or a low dose (20 mg/kg bw) administered after 14 days of dosing with non-radiolabelled test material (20 mg/kg bw). **Absorption:** The results indicate low absorption based on fecal radioactivity (>80% of the administered dose), but no biliary cannulation experiment or assessment of plasma kinetics was conducted. **Excretion:** 80-100% and 4-10% of the administered dose was excreted in feces and urine, respectively. The majority (80-90%) of the administered dose was excreted within the first 48 hours post-dosing. No major differences with respect to sex, dose regimen or radiolabel position were noted for the excretion profile. Radioactivity detected in expired air was negligible.

Study Type/Animal/PMRA #	Study Results
	Distribution: The highest levels of radioactivity were in the fat, liver and blood. The brain showed the lowest concentration of radioactivity. There were no major differences in the distribution of radioactivity between the two radiolabels. Levels of radioactivity in tissues of females were higher than males. Repeated exposure did not increase the level of radioactivity in tissues. Radioactivity levels in tissues in the high dose group were 5-6 times the values at the low dose. **Metabolism:** The parent compound was not detected in urine, but was the major compound detected in feces (40-70% of the administered dose). Urinary metabolites included M1, M2, M4, M5 and M6. Fecal metabolites included M8, M4, M5, M6, M7, M7A, M2 and M1. Metabolites identified in tissues included M2 (muscle), M3 (fat), M4 (muscle, kidney, liver), M5 (muscle, kidney, liver), M7 (fat, kidney, liver), M7A (liver), M8 (fat, muscle, kidney, liver). There were no major differences in metabolite profile in excreta or tissues with respect to sex, dose regimen or position of radioabel. The major metabolites were N-dealkylated (M4, M5, M7, M8), debrominated (M5 and M6) and hydroxylated (M4 and M7) products, and their conjugated forms (M1 and M2). The metabolic pathway appears to involve cleavage of the ethoxymethyl side-chain, followed by dealkylation and ring hydroxylation, and some degree of conjugation of the de-alkylated, ring-hydroxylated metabolites. The bond between the phenyl and pyrrole rings remains intact.

Table 4 Toxicity Profile of Metabolites of Chlorfenapyr

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/Metabolite/ PMRA #	Study Results
Acute oral toxicity Sprague Dawley Rats AC 312,094 PMRA #1859725	LD_{50} > 5000 mg/kg bw Low Toxicity

Study Type/Animal/Metabolite/ PMRA #	Study Results
Gene mutations in bacteria (Ames test) *S. typhimurium* strains: TA98, TA100, TA1535, TA1537 and TA1538; WP2 uvrA CL 303, 268 PMRA #1859787	Negative
Gene mutations in bacteria (Ames test) *S. typhimurium* strains: TA98, TA100, TA1535, TA1537 and TA1538; WP2 uvrA CL 312, 094 PMRA #1859788	Negative
Gene mutations in bacteria (Ames test) *S. typhimurium* strains: TA98, TA100, TA1535, TA1537 and TA1538; WP2 uvrA CL 322, 250 PMRA #1859789	Negative

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Chlorfenapyr

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	28-day dietary (mouse) and developmental toxicity (rabbit)	NOAEL = 30 mg/kg bw/day Mortality in adult animals within 2 days of dosing	100
	ARfD = 0.3 mg/kg bw		
Acute dietary females aged 13-49 and children up to 12 years	Developmental neurotoxicity study	NOAEL = 5 mg/kg bw/day Mortality, reduced motor activity, effects on learning and memory task in young animals	1000
	ARfD = 0.005 mg/kg bw		
Repeated dietary	Developmental neurotoxicity study	NOAEL = 5 mg/kg bw/day Mortality, reduced motor activity, effects on learning and memory task in young animals	1000
	ADI = 0.005 mg/kg bw/day		
Dermal – all durations[2]	Developmental neurotoxicity study	NOAEL = 5 mg/kg bw/day Mortality, reduced motor activity, effects on learning and memory task in young animals	1000
Inhalation – all durations[3]	90-Day inhalation study (rat)	NOAEL = 1.4 mg/kg bw/day Increased motor activity and rearing, decreased testes and epididymis weights; mortality at the next dose level.	1000
Non-dietary oral ingestion (short-term)	Developmental neurotoxicity study	NOAEL = 5 mg/kg bw/day Mortality, reduced motor activity, effects on learning and memory task in young animals	1000
Cancer	Low-dose linear extrapolation approach; Q_1* value of 1.56×10^{-2} [mg/kg bw/day]$^{-1}$ for histiocytic sarcomas in male rats		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 16% was used in a route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Nature Of The Residue In Plant Commodities

NATURE OF THE RESIDUE IN TOMATO			**PMRA # 1859801**	
Radiolabel Position	**^{14}C(phenyl) or ^{14}C(pyrrole) chlorfenapyr**			
Test Site	Field lots, Lucama, NC			
Treatment	Foliar broadcast spray to tomato plants			
Rate	0.20-0.21 kg a.i./ha × 5 applications			
Timing	from flowering and fruit setting stage to near harvest			
Preharvest interval	7 DAT and 14 DAT			
The study reported total radioactive residue (TRR) level in tomato leaves between 24 to 48 ppm, whereas in tomato fruits, TRR were much lower (0.03 to 0.05 ppm) evidence that there was limited translocation of chlorfenapyr within the plant. In tomato fruit, chlorfenapyr was the only significant residue component at 0.02 ppm representing 38-50% of the TRR of the [phenyl-^{14}C] labelled chlorfenapyr and 50% of the [pyrrole-^{14}C] labelled chlorfenapyr. There were several other unknown minor residue components that were characterized, each representing <0.01 ppm. The similar TRR results from the two ^{14}C labelled chlorfenapyr studies indicated that the bond between the phenyl ring and the pyrrole ring remained intact. A similar trend was observed in the immature and mature tomato leaves.				
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**^{14}C(phenyl)**	**^{14}C(pyrrole)**	**^{14}C(phenyl)**	**^{14}C(pyrrole)**
Tomato fruit	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)	--	--
NATURE OF THE RESIDUE IN COTTON			**PMRA # 1859798**	
Radiolabel Position	**^{14}C(phenyl) or ^{14}C(pyrrole) chlorfenapyr**			
Test Site	Field lots, Madera, CA			
Treatment	Foliar broadcast spray to cotton plants			
Rate	0.45-0.54 kg a.i./ha × 5 applications			
Timing	from mid-flowering stage to near harvest			
Preharvest interval	28 DAT5			
At 28 days PHI, TRR in the cottonseed (seed meal plus linters) was 0.27 ppm for the [pyrrole-14C] CL303,630 treatment and 0.31 ppm for the [phenyl-14C] CL303,630 treatment. The study reported total radioactive residue (TRR) level in cotton leaves between 38 to 132 ppm, evidence that there was a limited translocation of chlorfenapyr within the plant The result showed that chlorfenapyr (CL303,630) was the predominant residue component, which accounted for 59.3% to 67.7% (0.16 ppm to 0.21 ppm) of the TRR in cottonseed. The Unknown 1 metabolite accounted for 3.2% to 3.7% of the TRR (0.01 ppm). The minor metabolite Unknown 1 was characterized by P-glucosidase hydrolysis and by negative ion chemical ionization mass spectrometry as a non-glucoside and non-hydroxylated degradate of CL303,630. There were many other minor unknown metabolites with 14C radioactivity slightly above background, totalling 0.05 ppm to 0.06 ppm; however, none of the individual unknown				

metabolites exceeded 0.01 ppm. The results from two different labelled 14C-CL303,630 trials gave similar TRR and residue components, demonstrating that the bond between the phenyl and pyrrole ring was not cleaved. A similar trend was observed in the cotton leaves. TRR accumulated on cotton leaves after each treatment.

The nature of the residue in field-treated cotton is adequately understood.

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**^{14}C(phenyl)**	**^{14}C(pyrrole)**	**^{14}C(phenyl)**	**^{14}C(pyrrole)**
Cotton seed	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)	Unknown 1	Unknown 1
Seed meal	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)		
Seed linters	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)		

NATURE OF THE RESIDUE IN CITRUS	**PMRA # 1859799**
Radiolabel Position	**^{14}C(phenyl) or ^{14}C(pyrrole) chlorfenapyr**
Test Site	Field lots, Madera, CA
Treatment	Foliar broadcast spray to orange trees
Rate	0.74-0.75 kg a.i./ha × 3 applications
Timing	field grown four-year old naval orange trees - from early leaf stage to harvest
Preharvest interval	-7 DAT3 , 7 DAT3, 14 DAT3 and 28 DAT3

The TRR in the fruit harvested one week before the third treatment (-7 DAT3) ranged from 0.12 to 0.21 ppm, and the residue in the fruit harvested after the third treatment (7, 14 and 28 DAT3) decreased from 0.16-0.35 ppm to 0.10-0.13 ppm. TRR in the citrus fruit was distributed nearly all in the peel.

Chlorfenapyr was identified by HPLC analysis and confirmed by mass spectrometry as the predominant residue component in the organic extract, which accounted for 55-77% of the TRR (0.07-0.25 ppm) in citrus fruit. Other minor radioactive components included CL 303,268, CL 322,250 and CL 325,195, each accounting for < 3.3% of the TRR and less than 0.01 ppm. The consistent metabolic profile for treatments of both [phenyl-14C] and [2-pyrrole-14C] CL 303,630 at 14 DAT3 and 28 DAT3 demonstrated that the bond between the pyrrole ring and the phenyl ring was not cleaved.

The nature of the residue in citrus fruit is adequately understood.

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**^{14}C(phenyl)**	**^{14}C(pyrrole)**	**^{14}C(phenyl)**	**^{14}C(pyrrole)**
Citrus fruit	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)	CL303,268 CL322,250 CL325,195	CL303,268 CL322,250 CL325,195

NATURE OF THE RESIDUE IN LETTUCE			PMRA # 1859800	
Radiolabel Position	**^{14}C(phenyl) or ^{14}C(pyrrole) chlorfenapyr**			
Test Site	Field lots, Kerman, CA			
Treatment	Foliar broadcast spray to lettuce			
Rate	0.28 kg a.i./ha × 5 applications			
Timing	later growth stage to near harvest			
Preharvest interval	2-4 hours after treatment (i.e. 0 DAT5), 3 DAT5 and 7 DAT5			
At 3 days after last application, TRR in the lettuce with wrapper leaves peaked at 13.77 ppm for the [pyrrole-^{14}C] CL 303,630 treatment and 12.74 ppm for the [phenyl-^{14}C] CL 303,630 treatment. A lower residue level was found in the lettuce with wrapper leaves removed, where at 3 and 7 days after last application, TRR was 7.49 and 7.42 ppm, respectively, for the [pyrrole-^{14}C] CL 303,630 treatment and 5.37 and 8.89 ppm, respectively, for the [phenyl-^{14}C]-CL 303,630 treatment. The results showed that CL 303,630 was the predominant residue component in lettuce extracts which accounted for 75.1% (10.34 ppm) and 76.8% (9.78 ppm) of [2-pyrrole-14C] and [phenyl-14C] CL 303,630-derived TRR in lettuce, respectively. Metabolites CL 325,195, CL 303,268, and CL 312,094 accounted for 1.2 to 1.8% (0.17 to 0.23 ppm), 1.1 to 1.3% (0.14 to 0.18 ppm) and 0.8 to 1.4% (0.11 to 0.18 ppm) of TRR from both carbon-14 label treatments. Several minor radioactive unknowns (7 to 12) were detected and they accounted for 16.2 to 22% (1.61 to 2.06 ppm) of TRR. Trace unknown metabolites with 14C radioactivity less than twice the background of blank samples was not quantitated. No further attempts were made to characterize minor radioactive unknown metabolites. The nature of the residue in field-treated lettuce is adequately understood.				
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**^{14}C(phenyl)**	**^{14}C(pyrrole)**	**^{14}C(phenyl)**	**^{14}C(pyrrole)**
Lettuce foliage	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)	CL303,268 CL312,094 CL325,195	CL303,268 CL312,094 CL325,195
NATURE OF THE RESIDUE IN POTATO			**PMRA # 1859802**	
Radiolabel Position	**^{14}C(phenyl) or ^{14}C(pyrrole) chlorfenapyr**			
Test Site	Field lots, Lucama, NC			
Treatment	Foliar broadcast spray to potato			
Rate	0.15-0.19 kg a.i./ha × 4 applications			
Timing	later growth stage to near harvest			
Preharvest interval (DAT)	0 DAT1, 0 DAT2, 0 DAT3, 0 DAT4, 7 DAT4			
The metabolism of chlorfenapyr in potato was reviewed previously by PMRA (1995-0491/1995-0492) and it was concluded that 14C- residues did not accumulate in potato tubers (<0.003 ppm) at 7 days after four weekly applications of [phenyl -14C] and [2-pyrrole-14C] CL 303,630 totalling 0.57 to 0.77 kg a.i./ha, respectively. The TRR on the foliage increased after each application from 3.8 ppm to 43.2 ppm after the last application. A lower residue level of 7.99-				

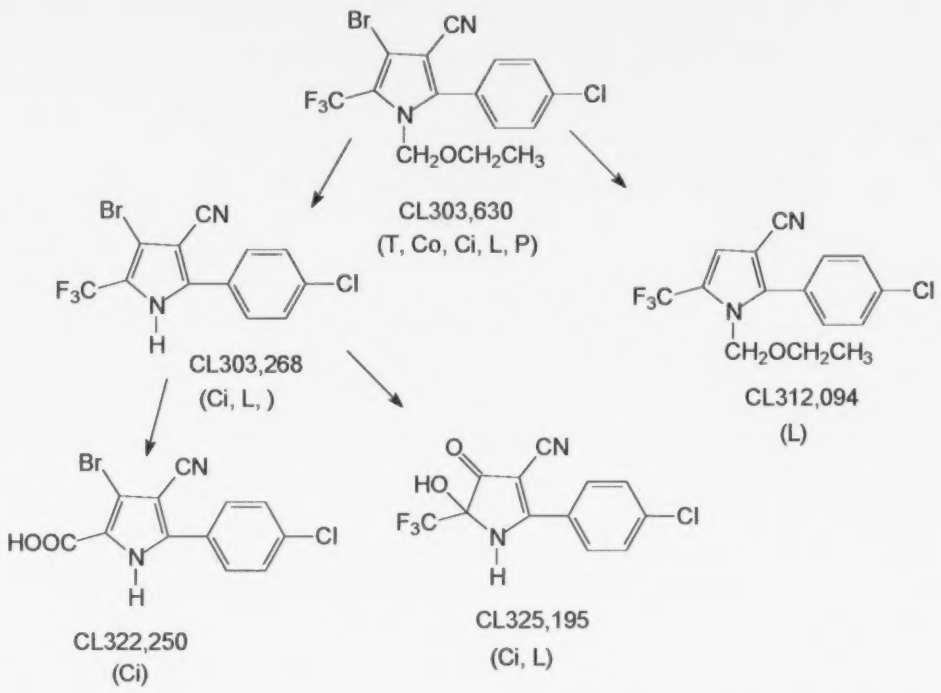
8.14 ppm was found in the potato vine.

The parent compound CL 303,630 was the only significant residue component identified in the potato foliage collected at zero day after the fourth application (0DAT4), which accounted for 74.7% (32.24 ppm) and 86.6% (31.32 ppm) of [2-Pyrrole-14C] and [Phenyl(U)-14C] CL 303,630-derived TRRs, respectively. The high TRR in foliage and vines and the TRR in the potato tubers below the detection limit, indicate that CL 303,630-derived radioactive residue was not translocated from foliage or soil surface to the tubers. The metabolic profile for the [2-pyrrole-14C] and [phenyl-14C] label CL 303,630 is similar in potato confirming that the bond between the phenyl and pyrrole ring apparently remained intact.

The nature of the residue in field-treated potato foliage is adequately understood.

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**^{14}C(phenyl)**	**^{14}C(pyrrole)**	**^{14}C(phenyl)**	**^{14}C(pyrrole)**
Potato foliage	Chlorfenapyr (CL303,630)	Chlorfenapyr (CL303,630)	--	--

Proposed metabolic scheme in tomato, cotton, citrus, lettuce and potato



The metabolism studies showed that the unchanged parent chlorfenapyr was the major residue component accounting for 38-77 % of the TRR in the studied crops, with minor metabolites being CL303,268; CL312,094; CL322,250 and CL325,195. In plants, chlorfenapyr undergoes reactions of *N*-dealkylation, debromination and hydroxylation without the cleavage of the phenyl-pyrrole ring bond.

Plant metabolism studies of chlorfenapyr conducted under greenhouse conditions are not available at this time. However, the submitted plant metabolism studies in the five diverse crops: cotton, citrus, lettuce, potato and tomato show a similar metabolic profile under field conditions. Therefore, it is expected that the greenhouse treated crops will have the same metabolic profile as the treated field crops.

Table 7 Storage Stability

STORAGE STABILITY	PMRA # 1859976
The freezer stability studies showed that chlorfenapyr residues were stable in the tested RACs and processed commodities for at least 24 months when stored in a freezer at approximately -10 to -20°C.	

Table 8 Greenhouse Residue Trials

CROP FIELD TRIALS ON GREENHOUSE FRUITING VEGETABLES	PMRA # 1859977, 1859978

Two tomatoes and one of each bell and non-bell pepper greenhouse trials were conducted during the 1998 growing season. Tomatoes and peppers were treated with five foliar broadcast applications of chlorfenapyr at application rates of 0.20-0.24 kg a.i./ha to a total of 1.11-1.14 kg a.i./ha/season equivalent to ~1.7-fold maximum seasonal GAP.

Non-ionic wetting adjuvants were added to the spray mixtures for any of the applications. Duplicate samples of tomato and pepper fruit were harvested 0.1-5 day after the last treatment.

Commodity	Total Rate (Kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
Tomato – greenhouse trials	0.224 × 5	0.1	2	0.23	0.34	-	-	0.29	-
		1	2	0.17	0.25	-	-	0.21	-
		3	2	0.24	0.25	-	-	0.25	-
		5	2	0.17	0.17	-	-	0.17	-
	0.228 × 5	0.1	2	0.26	0.31	-	-	0.29	-
		1	2	0.26	0.29	-	-	0.28	-
		3	2	0.24	0.29	-	-	0.27	-
		5	2	0.12	0.20	-	-	0.16	-
Non-bell pepper – greenhouse trials	0.226 × 5	0.1	2	0.60	0.65	-	-	0.63	-
		1	2	0.49	0.69	-	-	0.59	-
		3	2	0.60	0.63	-	-	0.62	-
		5	2	0.28	0.46	-	-	0.37	-
Bell pepper – greenhouse trials	0.222 × 5	0.1	2	0.31	0.39	-	-	0.35	-
		1	2	0.39	0.43	-	-	0.41	-
		3	2	0.28	0.45	-	-	0.37	-
		5	2	0.36	0.36	-	-	0.36	-

Table 9 Processed Food

PROCESSED FOOD	PMRA # 1933082

A processing study was requested to address the potential residues in tomato processed commodities. The applicant indicated that greenhouse tomatoes are not typically processed due to their high market value.

Table 10 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (greenhouse fruiting vegetables)** **Rotational crops**	Chlorfenapyr N/A
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (greenhouse fruiting vegetables)** **Rotational crops**	Chlorfenapyr N/A
METABOLIC PROFILE IN DIVERSE CROPS	The metabolic profile was shown to be similar for five diverse crops. It is assumed that the metabolic profile will be similar in all crops.
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	N/A
RESIDUE DEFINITION FOR RISK ASSESSMENT	N/A
METABOLIC PROFILE IN ANIMALS	N/A
FAT SOLUBLE RESIDUE	N/A

Table 11 Dietary Exposure and Risk Assessment

DIETARY RISK FROM FOOD		
Intermediate acute dietary risk **ARfD = 0.3 mg/kg bw** **aPAD = 0.005 mg/kg bw for children <12 years and females 13-49 years**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**
		Food Only
	General Population	N/A
	All infants (< 1 year)	0.36
	Children 1-2 yrs	**20.93**
	Children 3-5 yrs	20.09
	Children 6-12 yrs	15.97
	Males 13-19 yrs	0.21
	Males 20+ yrs	0.26
	Adults 50+ yrs	0.25
	Females 13-49 yrs	14.26

DIETARY RISK FROM FOOD		
Basic chronic non-cancer dietary risk **ADI = 0.1 mg/kg bw** **Estimated chronic drinking water concentration = 1.6 µg a.i./L**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food Only
	General Population	18.0
	All infants (< 1 year)	3.6
	Children 1-2 yrs	19.9
	Children 3-5 yrs	20.5
	Children 6-12 yrs	17.8
	Youth 13-19 yrs	15.3
	Adults 20-49 yrs	18.7
	Adults 50+ yrs	18.2
	Females 13-49 yrs	17.2
Refined cancer dietary risk	**POPULATION**	**ESTIMATED RISK**
		Food Only
	General Population	9×10^{-8}

Table 12 Fate and Behaviour of Chlorfenapyr in the Terrestrial Environment

Study Type	Test substance	Value	Transformation products	Comments
Abiotic transformation				
Hydrolysis	**TGAI**: AC 303,630 (chlorfenapyr)	Stable at pH 5, pH 7, pH9	None	Not a route of transformation
Photo-transformation on soil	**TGAI**: AC 303,630 (chlorfenapyr)	^{14}C-Phenyl label – half-life = 67 days (SFO) ^{14}C-Pyrrole label – Half-life = 77 days (SFO)	- No Major TP - Minor TP: 325,195 (~ 5% AR) 303,268 (~5% AR) - additional uknowns (≤ 3% AR)	Experimental condition: continuous irradiation. Not an important route of transformation
Biotransformation				
Bio-transformation in aerobic soil **Sandy loam soil** from New	**TGAI**: AC 303,630 (chlorfenapyr)	Both ^{14}C-Phenyl and ^{14}C-Pyrrole labels – Half-life	- No Major TP - Minor TP's not identified	Very persistent

Study Type	Test substance	Value	Transformation products	Comments
Jersey (pH 5.4, organic carbon 0.6%)		= 1370 days (SFO)		
Sandy loam soil from New Jersey (pH 6.8, organic carbon 0.87%)	**TGAI**: AC 303,630 (chlorfenapyr)	DT_{50} = 1180 days (DFOP)	- No Major TP Minor TP's: CL 312094, CL 303267, CL 303268, and CL 325195 (1-~8% AR)	Very persistent
	TGAI: AC 303,630 (chlorfenapyr)	DT_{50} = 3670 days (DFOP)	- No Major TP's - same minor TP's	Very persistent
Sandy loam soil from North Carolina (pH 6.3, organic carbon 1.33%)	**TGAI**: AC 303,630 (chlorfenapyr)	Half-life = 239 days (SFO)	- No Major TP's - same minor TP's	Persistent
Clay from Texas (pH 8.1, organic carbon 1.62%)	**TGAI**: AC 303,630 (chlorfenapyr)	Half-life = 392 days (SFO)	- No Major TP's - same minor TP's	Persistent
Sandy Loam soil from Mississippi (pH 6.3, organic carbon 0.46%)		Half-life = 349 days (SFO)	- No Major TP's - same minor TP's	
Sandy Loam soil from California (pH 5.9, organic carbon 0.46%)				

Study Type	Test substance	Value	Transformation products	Comments
Biotransformation in anaerobic soil **Sandy loam soil** from New Jersey (pH 5.4, organic carbon 0.6%)	**TGAI**: AC 303,630 (chlorfenapyr)	Both ^{14}C-Phenyl and ^{14}C-Pyrrole labels – Half-life = 670 days (SFO)	- No Major TP - Several Minor TP's; none identified	Persistent
Mobility				
Adsorption to soil (Linear, non-Freundlich K_{oc} values)	**TGAI**: 303,630 (chlorfenapyr)	Arkansas Loamy Sand – K_{oc} = 13214	N/A	Immobile
		Indiana Silt Loam – K_{oc} = 180905	N/A	Immobile
		New Jersey Sandy Loam – K_{oc} = 14177	N/A	Immobile
		Wisonsin Loam – K_{oc} = 12321	N/A	Highly mobile
	TP: CL 325,195	Arkansas Loamy Sand – K_{oc} = 125	N/A	Moderately mobile
		Indiana Silt Loam – K_{oc} = 248	N/A	Highly mobile
		New Jersey Sandy Loam – K_{oc} = 107	N/A	Highly mobile
		Wisonsin Loam – K_{oc} = 66	N/A	

Study Type	Test substance	Value	Transformation products	Comments
		North Carolina Sandy Loam – K_{oc} = 150		Highly mobile

Table 13 Fate and Behaviour of Chlorfenapyr in the Aquatic Environment

Study type	Test material	Value	Transformation products	Comments
Abiotic transformation				
Hydrolysis	**TGAI**: 303,630 (chlorfenapyr)	Stable at pH 5, pH 7, pH 9	None	Not a route of transformation
Phototransformation in water	**TGAI**: 303,630 (chlorfenapyr)	Both ^{14}C-Phenyl and ^{14}C-Pyrrole labels – 4.2, 8 and 22 days at pH 5, pH 7 and pH 9 (SFO)	Major TP: 357,806 (53-66% AR)	Experimental Condition: Continuous irradiation. TP is a regio-isomer of parent compound.
Biotransformation				
Biotransformation in aerobic water systems **Sandy Sediment System** (sediment pH 8.4, organic carbon 0.2%)	**TGAI**: 303,630 (chlorfenapyr)	^{14}C-Pyrrole label – Half-life = 223 days (SFO) ^{14}C-Phenyl label – Half-life = 218 days (SFO)	- No major or minor TP's identified - No major or minor TP's identified	Persistent Persistent
Loamy Sediment System (sediment pH 6.6, organic carbon 6.7%)	**TGAI**: 303,630 (chlorfenapyr)	^{14}C-Pyrrole label – Half-life = 226 days (SFO)	- Major TP: CL312,094 (19% AR) - No minor TP's identified - Major TP:	Persistent Persistent

Study type	Test material	Value	Transformation products	Comments
		^{14}C-Phenyl label – Half-life = 418 days (SFO)	CL312,094 (19% AR) - No minor TP's identified	
Biotransformation in anaerobic water systems **Sandy Sediment System** (sediment pH 7.1, organic carbon 1.4%) mg/L; sediment pH 7.3, organic carbon 2.4%)	**TGAI**: 303,630 (chlorfenapyr)	^{14}C-Pyrrole label – Total system DT_{50} = 202 days (DFOP) Half-life in Sediment = 196 days (SFO) DT_{50} in water = 5.5 days (IORE)	- Major TP: CL 312,094 (24.5% AR on day 365) - Minor TP's: not identified (0.1 – 2.2% AR)	Persistent
Partitioning				
Bioaccumulation in Fish	**TGAI**: 303,630 (chlorfenapyr)	Steady State BCF Values– Whole Fish: 97 14.2 mL/g	N/A	Not expected to bioconcentrate in fish.

Table 14 Screening Level Risk Assessment for Honey Bees

Organism	Exposure	Test Substance (g a.i./ha)	Ecotox Endpoint Value (g a.i./ha)	EEC (g a.i./ha)	RQ (EEC / LD_{50})	LOC Exceeded
Honey bee, *Apis mellifera*	Contact	TGAI: AC 303,630 at 35 - 1067 g a.i./ha	96-hour LD_{50} = 370 g a.i./ha	**Maximum Cumulative Rate** Ornamentals: 848 g a.i./ha	2.3	Yes

Organism	Exposure	Test Substance (g a.i./ha)	Ecotox Endpoint Value (g a.i./ha)	EEC (g a.i./ha)	RQ (EEC / LD_{50})	LOC Exceeded
				Vegetables: 1006 g a.i./ha **Maximum Single Rate** Ornamentals: 561.6 g a.i./ha Vegetables: 456 g a.i./ha	2.8 1.5 1.3	Yes Yes Yes
Honey bee, *Apis mellifera*	Oral	TGAI: AC 303,630 at 130 – 4290 g a.i./ha	96-hour LD_{50} = 1120 g a.i./ha	**Maximum Cumulative Rate** Ornamentals: 848 g a.i./ha Vegetables: 1006 g a.i./ha **Maximum Single Rate** Ornamentals: 561.6 g a.i./ha Vegetables: 456 g a.i./ha	0.77 0.91 0.5 0.4	No No No No

Table 15 Refined Risk Assessment for Honey Bees Using the Minimum Spray Volume, as well as the Minimum and Maximum Application Rate, to Obtain the Lower Range of EEC Values for Small Bedding Plants and Small Tomatoes

Organism/ Exposure; Test substance	Ecotox Endpoint Value (g a.i./ha)	Crop	Minimum Required Spray Volume	EEC (g a.i. / ha)	RQ (EEC/LD_{50}) or (EEC/LR_{50})	LOC Exceeded
POLLINATORS – Honey Bees						

Organism/ Exposure; Test substance	Ecotox Endpoint Value (g a.i./ha)	Crop	Minimum Required Spray Volume	EEC (g a.i. / ha)	RQ (EEC/LD_{50}) or (EEC/LR_{50})	LOC Exceeded
Honey bee/ Contact; TGAI	370 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 289 Min: 38	0.78 0.10	No No
		Fruiting Vegetables: small tomatoes only	285 285	Max: 143 Min: 31	0.39 0.085	No No
Honey bee/ Oral; TGAI	1120 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 289 Min: 38	0.26 0.035	No No
"	"	Fruiting Vegetables: small tomatoes only	285 285	Max: 143 Min: 31	0.13 0.028	No No

Table 16 Screening Level Risk Assessment for Beneficial Arthropods

Organism	Exposure	Test Substance (g a.i./ha)	Ecotox Endpoint Value (g a.i. / ha)	EEC (g a.i. / ha)	RQ (EEC / LR_{50})	LOC Exceeded
Predatory mite, *Typhlodromus pyri*	Contact (glass box)	TGAI: AC 303,630 at 265 g a.i./ha	24-hour LR_{50} is < 265 g a.i./ha	Ornamentals: 848 g a.i./ha Vegetables: 1006 g a.i./ha	> 3.2 > 3.8	Yes Yes
Parasitic wasp, *Aphidius matricariae* HAL	Contact (glass plate)	TGAI: AC 303,630 at 262 g a.i./ha	24-hour LR_{50} is < 262 g a.i./ha	Ornamentals: 848 g a.i./ha Vegetables: 1006 g a.i./ha	> 3.2 > 3.8	Yes Yes
Predatory bug, *Orius insidiosus*	Contact (glass box)	EP: (240 g/L) at 217 g a.i./ha	24-hour $LR_{50}$is < 217 g a.i./ha	Ornamentals: 848 g a.i./ha Vegetables: 1006 g a.i./ha	> 3.9 > 4.6	Yes Yes
Ladybird beetle,	Contact (glass	TGAI: AC	24-hour $LR_{50}$is < 199	Ornamentals: 1149 g a.i./ha	> 5.8	Yes

Organism	Exposure	Test Substance (g a.i./ha)	Ecotox Endpoint Value (g a.i. / ha)	EEC (g a.i. / ha)	RQ (EEC / LR_{50})	LOC Exceeded
Coccinella septempunctata	plate)	303,630 at 199 g a.i./ha	g a.i./ha	Vegetables: 1365 g a.i./ha	> 6.9	Yes
Carabid beetle, *Poecilus cupreus*	Contact (quartz sand)	TGAI: AC 303,630 at 545 g a.i./ha	96-hour LR_{50} is < 545 g a.i./ha	Ornamentals: 1149 g a.i./ha Vegetables: 1365 g a.i./ha	> 2.1 > 2.5	Yes Yes
Predatory mite, *Typhlodromus pyri*	Contact (field study)	EP: (240 g/L) at 302 g a.i./ha	There was an 84% reduction in the number of mites in chlorfenapyr-treated plots versus controls on Day 35. On Day 59, the reduction relative to controls was 30%.			

Table 17 Refined Risk Assessment for Beneficial Arthropods Using the Minimum Spray Volume, as well as the Minimum and Maximum Application Rate, to Obtain the Lower Range of EEC Values for Small Bedding Plants and Small Tomatoes

Organism / Exposure; Test substance	Ecotox Endpoint Value (g a.i./ha)	Crop	Minimum Required Spray Volume	EEC (g a.i. / ha)	RQ (EEC / LD_{50}) or (EEC / LR_{50})	LOC Exceeded
BENEFICIAL ARTHROPODS						
Predatory mite / Contact (glass box); TGAI	24-hour LR_{50} is < 265 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 289 Min: 38	> 1.09 > 0.14	Yes Uncertain
		Fruiting Vegetables: small tomatoes only	285 285	Max: 143 Min: 31	> 0.54 > 0.12	Uncertain Uncertain
Parasitic wasp Contact (glass plate); TGAI	24-hour LR_{50} is < 262 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 289 Min: 38	> 1.10 > 0.15	Yes Uncertain
		Fruiting Vegetables: small tomatoes only	285 285	Max: 143 Min: 31	> 0.55 > 0.12	Uncertain Uncertain

Organism / Exposure; Test substance	Ecotox Endpoint Value (g a.i./ha)	Crop	Minimum Required Spray Volume	EEC (g a.i. / ha)	RQ (EEC / LD_{50}) or (EEC / LR_{50})	LOC Exceeded
Predatory bug/ Contact (glass box); EP	24-hour LR_{50} is < 217 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 289 Min: 38	> 1.33 > 0.18	Yes Uncertain
		Fruiting Vegetables: small tomatoes only	285 285	Max: 143 Min: 31	> 0.66 > 0.14	Uncertain Uncertain
Ladybird beetle/ Contact (glass plate); TGAI	24-hour LR_{50} is < 199 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 392 Min: 51	> 1.97 > 0.26	Yes Uncertain
		Fruiting Vegetables: small tomatoes only	285 285	Max: 195 Min: 42	> 0.98 > 0.21	Uncertain Uncertain
Carabid beetle/ Contact (glass plate); TGAI	96-hour LR_{50} is < 545 g a.i./ha	Ornamentals: small bedding plants only	350 350	Max: 392 Min: 51	> 0.72 > 0.09	Uncertain Uncertain
		Fruiting Vegetables: small tomatoes only	285 285	195 42	> 0.36 > 0.08	Uncertain Uncertain

Table 18 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes. 1670 days (80^{th} percentile value of aerobic soil biotransformation studies)

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
	Water	Half-life ≥ 182 days	No. 5.5 days (anaerobic aquatic biotransformation study)
	Sediment	Half-life ≥ 365 days	Yes. 196 days (sediment) 202 days (total system) (anaerobic aquatic biotransformation study)
	Air	Half-life ≥ 2 days or evidence of long range transport	No. Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure ($<5.4 \times 10^{-6}$ Pa) and Henry's law constant (8.22×10^{-6} atm-m^3- mol^{-1}).
Bioaccumulation[4]	Log $K_{ow} \geq 5$		Yes. 5.24
	BCF ≥ 5000		No. 97 (whole fish)
	BAF ≥ 5000		Data not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No. Does not meet all four TSMP Track 1 criteria.

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Table 19 Alternative Insecticide Active Ingredients for Mythic Insecticide in USC 20: Structural and USC 21: Structures and Surrounding Soil.

Pest	Mode of Action Group	Alternative Insecticide Active Ingredients Include
Ants	1A: Carbamates	Bendiocarb; Propoxur
	1B: Organophosphates	Chlorpyrifos; Dichlorvos; Malathion; Propetamphos
	3A: Pyrethroids, Pyrethrins	Cyfluthrin; D-cis, trans allethrin; D-phenothrin; D-trans allethrin; Imiprothrin; Lambda-cyhalothrin; Permethrin; Prallethrin; Pyrethrins; Resmethrin; Tetramethrin
	6: Avermectins, Milbemycins	Abamectin
	8D: Borax	Borax
	20A: Hydramethylnon	Hydramethylnon
	Other:	Boracic acid; Disodium octaborate tetrahydrate; Silica aerogel; Silicon dioxide

Pest	Mode of Action Group	Alternative Insecticide Active Ingredients Include
House flies	1A: Carbamates	Methomyl; Naled; Propoxur
	1B: Organophosphates	Azamethiphos; Chlorpyrifos; Dichlorvos; Dimethoate; Malathion; Tetrachlorvinphos; Trichlorfon
	3A: Pyrethroids, Pyrethrins	Cyfluthrin; D-cis, trans allethrin; D-trans allethrin; D-phenothrin; Lambda-cyhalothrin; Permethrin; Pyrethrins; Resmethrin; Tetramethrin
	4A: Neonicotinoids	Thiamethoxam
	Pheromone	(Z)-9-tricosene
	Microbial	*Beauveria bassiana* strain HF 23
	Other:	Silicon dioxide
Spiders	1A: Carbamates	Bendiocarb; Propoxur
	1B: Organophosphates	Chlorpyrifos; Malathion; Propetamphos
	3A: Pyrethroids, Pyrethrins	Cyfluthrin; D-cis, trans allethrin; D-phenothrin; D-trans allethrin; Imiprothrin; Lambda-cyhalothrin; Permethrin; Prallethrin; Pyrethrins; Resmethrin; Tetramethrin
	Other:	Boracic acid; D-limonene; Silicon dioxide; Silica aerogel
Paper wasps	1A: Carbamates	Bendiocarb; Propoxur
	1B: Organophosphates	Chlorpyrifos; Dichlorvos; Malathion
	3A: Pyrethroids, Pyrethrins	Cyfluthrin; D-cis, trans allethrin; D-phenothrin; D-trans allethrin; Lambda-cyhalothrin; Permethrin; Pyrethrins; Resmethrin; Tetramethrin
	Other:	Silicon dioxide
Asian lady beetles	3A: Pyrethroids, Pyrethrins	Cyfluthrin; Pyrethrins
	Other:	D-limonene; Silicon dioxide
Boxelder bug	1A: Carbamates	Propoxur
	1B: Organophosphates	Chlorpyrifos
	3A: Pyrethroids, Pyrethrins	D-cis, trans allethrin; Lambda-cyhalothrin; Permethrin; Pyrethrins; Tetramethrin
	Other:	Disodium octoborate tetrahydrate; Silicon dioxide
Centipede	1A: Carbamates	Bendiocarb; Propoxur
	1B: Organophosphates	Chlorpyrifos
	3A: Pyrethroids, Pyrethrins	D-cis, trans allethrin; D-phenothrin; D-trans allethrin; Lambda-cyhalothrin; Permethrin; Pyrethrins; Resmethrin; Tetramethrin
	Other:	Boracic acid; D-limonene; Silicon dioxide
European earwig	1A: Carbamates	Bendiocarb; Carbaryl; Propoxur
	1B: Organophosphates	Chlorpyrifos; Malathion; Propetamphos
	3A: Pyrethroids, Pyrethrins	Cyfluthrin; D-cis, trans allethrin; D-trans

Pest	Mode of Action Group	Alternative Insecticide Active Ingredients Include
		allethrin; D-phenothrin; Lambda-cyhalothrin; Permethrin; Pyrethrins; Resmethrin; Tetramethrin
	Other:	Boracic acid; Disodium octoborate tetrahydrate; Silicon dioxide
House cricket	1A: Carbamates	Bendiocarb; Carbaryl; Propoxyr
	1B: Organophosphates	Chlorpyrifos; Malathion; Propetamphos
	3A: Pyrethroids, Pyrethrins	Cyfluthrin; D-cis, trans allethrin; D-phenothrin; D-trans allethrin; Imiprothrin; Lambda-cyhalothrin; Permethrin; Prallethrin; Pyrethrins; Tetramethrin
	Other:	Boracic acid; D-limonene; Disodium octoborate tetrahydrate; Silicon dioxide; Silica aerogel
Pillbug	1A: Carbamates	Bendiocarb
	1B: Organophosphates	Chlorpyrifos; Propetamphos
	3A: Pyrethroids, Pyrethrins	Permethrin; D-cis, trans allethrin; Pyrethrins ; Tetramethrin
	Other:	Boracic acid; Silicon dioxide
Silverfish	1A: Carbamates	Bendiocarb
	1B: Organophosphates	Chlorpyrifos; Malathion; Propetamphos
	3A: Pyrethroids, Pyrethrins	D-cis, trans allethrin; Disodium octoborate tetrahydrate; D-trans allethrin; D-phenothrin; Lambda-cyhalothrin; Permethrin; Pyrethrins; Tetramethrin
	Other:	Boracic acid; Silica aerogel; Silicon dioxide
Termites	1A: Carbamates	Propoxur
	3A: Pyrethroids, Pyrethrins	Lambda-cyhalothrin; Permethrin
	Other:	Disodium octoborate tetrahydrate

Table 20 Pylon Miticide Insecticide Acceptable Use Claims

Crop	Acceptable use pattern/claims				
	Pest	**Rate (ml/100L) (g a.i./ 100 L)**	**Max. no. of applications per crop cycle**	**Minimum reapplication interval**	**Maximum spray volume (L/ha)**
Greenhouse ornamentals (including but not limited to African violet, geranium and petunia)	Two-spotted spider mite	20-41 (4.8-9.8)	3	5 days	1500
	Cabbage looper Soybean looper	30-50 (7.2-12)			
	Foliar nematodes	41-78 (9.8-18.7)			
	Western flower thrips	78-156 (18.7-37.4)			
Tomato Tomatillo Ground cherry Pepper Eggplant Pepino	Tomato hornworm Tobacco budworm Cabbage looper Alfalfa looper	30 (7.2)	1	N/A	1000
	Two-spotted spider mite	20-30 (4.8-7.2)			
No unacceptable injury has occurred to the following greenhouse ornamental plants when treated with Pylon Miticide Insecticide according to label instructions: African daisy African violet Aster Azalea Begonia Chrysanthemum Croton Gardenia Lisianthus Miniature rose Verbena					

Table 21 Mythic Insecticide Acceptable Use Claims

Pest	Acceptable use pattern/claims		
	Method of application	**Concentration (% a.i.)**	**Max. Rate (mL dilution/m^2)**
Ants	Crack and crevice; Spot	0.125-0.25%	190
Asian ladybird beetle	Crack and crevice; Spot	0.25% a.i.	
Boxelder bugs			
Centipedes			
European earwig			
House crickets			
Paper wasps			
Pillbugs			
Silverfish			
Spiders			
House flies	Crack and crevice Spot	0.50% a.i.	
Termites (pre-construction and post-construction)	Rodding, trenching, injection, treated back fill	0.125-0.25% a.i.	Rate dependent on type of construction: 3.8 L dilution / 0.9 m^2; or 15 L dilution / 3 linear , / 0.3 m deep; or 7.5 / 3 linear m; or 3.8 – 15 L dilution / 0.09 m^2 or 3.8 L dilution / 0.03 m^3
Termites (above ground nests)	Injection	0.125 to 0.25% a.i.	n/a

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

The proposed Canadian MRLs are not consistent with those in the U.S. Codex MRLs are not currently established for chlorfenapyr on any commodities.

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Fruiting vegetables: tomato, tomatillo, ground cherry, pepper, eggplant and pepino	2.0	1.0	Not reviewed by Codex

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1859691	2001, Product chemistry data requirements for the manufacturing-use product technical AC 303268: OPPTS 830.1600, Description of materials used to produce product and OPPTS 830.1620, description of production process, DACO: 2.11.1, 2.11.2, 2.11.3 CBI
1859693	2001, Process comparison and chemical equivalency information for Chlorfenapyr, DACO: 2.11.1, 2.11.3 CBI
1859694	2009, Minor Modification to Manufacturing Process and Starting materials, DACO: 2.11.2, 2.11.3 CBI
1859697	2002, Product chemistry data requirements for the manufacturing-use product, Technical AC 303,268: OPPTS 830.1670, Description of the formation of impurities, DACO: 2.11.4 CBI
1859698	2001, Compositional analysis of chlorfenapyr (AC 303,630, BAS 306 I) technical grade active ingredient manufactured at [CBI removed] in support of registration with world-wide regulatory auth, DACO: 2.12.
1921524	1993, Validation of the High Resolution Gas Chromatographic Method M-2006.1 to Assay for CL 303,630 in Pirate Technical Grade Active Ingredient (TGAI), DACO: 2.13.1 CBI
1921525	1993, Validation of the High Performance Liquid Chromatographic Method M-2066.01 to Assay for CL 303,268 in Pirate Technical Grade Active Ingredient (TGAI), DACO: 2.13.1 CBI
1921528	1993, Validation of the High Resolution Gas Chromatographic (HRGC) Method M-2272 to Assay for Impurities in Pirate Technical Grade Active Ingredient (TGAI), DACO: 2.13.1 CBI
1921532	1994, Validation of Gas Chromatographic Method M-2368 for Analysis of Residual Isopropanol and Xylenes in CL 303,630 Technical Grade Active Ingredient (TGAI), DACO: 2.13.1 CBI
1859699	1995, Identification of the Impurities in AC 303,630 technical grade active ingredient, DACO: 2.13.2 CBI
1939503	2010, Plant data, DACO: 2.13.3 CBI

1859701	1994, Product chemistry determinations for CL 303,630 purified (color, physical state, odor, density), DACO: 2.14.1, 2.14.2, 2.14.3, 2.14.6
1859700	1993, Pirate technical (AC 303,630) - Color, physical state, odor, bulk density, pH, oxidizing/reducing properties, DACO: 2.14.1, 2.14.2, 2.14.3, 2.14.6
1859714	1991, AC 303,630: Determination of the melting point, DACO: 2.14.4
1859715	1994, AC 303,630: Determination of the melting point, DACO: 2.14.4
1859717	2004, Relative density of Chlorfenapyr (BAS 306 I) - PAI and TGAI, DACO: 2.14.6
1859718	1994, AC 303,630: The determination of the solubility, DACO: 2.14.7, 2.14.8
1859720	1997, AC 303630: Determination of the vapor pressure, DACO: 2.14.9
1859707	1995, AC 303,630: n-octanol/water partition, DACO: 2.14.11
1859709	1994, CL 303,630 spectral database., DACO: 2.14.12 CBI
1859721	1993, Pirate technical (AC 303,630) - Explodability, DACO: 2.16
1859711	1994, Pirate technical (AC 303,630) - Storage stability, corrosion characteristics, and stability at normal and elevated temperatures, DACO: 2.14.13, 2.14.14
1859939	2009, Phantom terMiticide Insecticide, Pylon Miticide Insecticide (BAS 306 02 I) Group A - product identity, composition, and analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2 CBI
1859940	1993, Pirate and Stalker insecticides: Validation of a chromatographic method for the determination of the active ingredient CL 303,630 in suspension concentrate (SC) formulations, DACO: 3.4.1 CBI
1859941	1993, Pirate (AC303,630 3SC) insecticide product chemistry: Physical and chemical characteristics, DACO: 3.5
1859942	1994, AC 303,630 2SC insecticide product chemistry: Physical and chemical characteristics, DACO: 3.5.1, 3.5.12, 3.5.14, 3.5.2, 3.5.6, 3.5.7, 3.5.8, 3.5.9
1859948	2009, DACO 3.5.4 Formuation type, DACO: 3.5.4
1859949	2009, DACO 3.5.5 Container Material and Description, DACO: 3.5.5
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3.0 Environment

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B. Additional Information Considered

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2.0 Environment

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3.0 Environment

4.0 Value